U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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PUBLIC MEETING ON OVERSIGHT OF LABORATORY DEVELOPED TESTS

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MONDAY, JULY 19, 2010

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The meeting came to order at 8:00 a.m. in the Auditorium of the Marriott Inn and Conference Center, UMUC, 3501 University Boulevard East, Hyattsville, Maryland, Alberto Gutierrez presiding.

PRESENT:
ALBERTO GUTIERREZ, PhD, Director, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH
JOSHUA SHARFSTEIN, MD, Principal Deputy Commissioner, Food and Drug Administration
JEFFREY SHUREN, MD, JD, Director, Center for Devices and Radiological Health, FDA
COURTNEY HARPER, PhD, Director, Division of Chemistry and Toxicology Devices, CDRH
SALLY HOJVAT, PhD, Director, Division of Microbiology Devices, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH
ELIZABETH MANSFIELD, PhD, Director for Personalized Medicine, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH

PRESENT: (continued)

GINETTE MICHAUD, MD, Deputy Director for Science and Medicine, OBRR, CBER

KATHERINE SERRANO, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH

ALSO PRESENT:

PUBLIC PRESENTATION SESSION 1:

ROGER KLEIN, MD, Blood Center of Wisconsin, Medical College of Wisconsin
CARA TENENBAUM, Ovarian Cancer National Alliance
RICHARD HOCKETT, MD, Affymetrix
SHARON TERRY, MA, Genetic Alliance
BENJAMIN SALISBURY, PhD, PGxHealth, LLC
ERIC LAWSON, Voisin Life Sciences
DAN O'LEARY, Ombu Enterprises, LLC
ELIZABETH KEARNEY, National Society of Genetic Counselors
DANIEL POSCOVER, Posky LLC
MICHAEL STOCUM, Personalized Medicine Partners
DEIRDRE ASTIN, New York State Department of Health, Wadsworth Center
MARY PENDERGAST, Pendergast Consulting
JUDITH WILBER, PhD, XDx
STEVE WILLIAMS, MD, SomaLogic
WINTON GIBBONS, Nanosphere, Inc.
JOHN G. BARTLETT, MD, Infectious Diseases Society of America
MARK LINDER, PhD, PGXL Laboratories
JANET TRUNZO, Advanced Medical Technology Association (AdvaMed)
SARA KENKARE-MITRA, PhD, Genentech
SAURABH AGGARWAL, Parexel

SESSION 1 DISCUSSION:

BRENDA EVELYN, SBB (ASCP), Office of Special Health Issues, Food and Drug Administration, Session Moderator
STEVE GUTMAN, MD, MBA, Blue Cross and Blue Shield Association
COL. ALAN J. MAGILL, MD, FACP, FIDSA, Walter Reed Army Institute of Research
PAUL RADENSKY, MD, JD, McDermott, Will & Emery LLP
CARA TENENBAUM, ESQ. Ovarian Cancer National Alliance

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P R O C E E D I N G S

Time: 8:03 a.m.

DR. SHUREN: Good morning. I am Jeff Shuren, FDA's Director of the Center for Devices and Radiological Health, and I would like to welcome you to FDA's two-day Public Meeting on Laboratory Developed Tests or LDTs.

I would like to take a few moments just to go over the format for the meeting. This morning, we are going to start off with opening remarks from Dr. Joshua Sharfstein, FDA's Principal Deputy Commissioner.

That will be followed by three FDA presentations, which will provide context for the Public meeting. The presentations will review how the agency currently regulates in vitro diagnostics, as well as provide the agency's history and experience with LDTs.

The remainder of the meeting will be divided into four sessions, each session seeking to gain input from stakeholders on different issues related to oversight of LDTs. These sessions include patient and clinical considerations, clinical laboratory challenges, directed consumer testing, and education and outreach.

The first part of each session will be presentations

provided by the public to share their perspective on FDA oversight of LDTs. The second portion of each session will be a discussion in which a session moderator as well as the public audience will have the opportunity to pose questions to be discussed among invited commentators.

For those interested in lunch, there are options available, and there is information outside at the registration desk.

Please note that during the public presentations, we ask that each presenter present for only five minutes, and Katie Serrano will provide more details at the beginning of each session.

Let me close by saying that, although FDA has decided to exercise authority over LDTs, we have not made any decisions about how we will exercise that authority. That is what this two-day Public Meeting is about. We want to hear from you.

Following this meeting, we will consider those comments as well as comments submitted to the public docket, which closes on August 15th, before proceeding.

It is our hope to move forward with a framework over the next few months, and that will be put out for public comment before we move forward to finalize.

With that, let me turn to Dr. Sharfstein opening remarks.

DR. SHARFSTEIN: Thank you. Good morning. I will tell you that one more time. Good morning. I got to get everybody ready. You don't know whether the most exciting thing will be the first thing this morning. So you have to be on your toes at this meeting.

This is, obviously, a very important topic for the FDA to be tackling. I am sure that many of you are familiar with the recent article that Dr. Margaret Hamburg, the FDA Commissioner, and Dr. Francis Collins, the NIH Director, wrote in the New England Journal about personalized medicine.

If you read that, you know that from our perspective the area of personalized medicine is an area with tremendous public health value, and also in that area some public health risk.

The value comes from being able to give -- for patients to be able to get information about their risks, for doctors and patients to be able to better choose therapies, and the risks can come if information is wrong or misleading or leads to bad medical decisions.

The goal of regulation is to find the right approach to maximize the public health value and minimize the risk. I think one of the factors to consider there is how, in a regulatory

structure, it incentivizes the kind of research that gives good data that helps people to really make good decisions.

I would recommend people, if they have some time on their hands, to read an interesting book about FDA regulation over the last century called "Power and Reputation" by Daniel Carpenter, because it talks about some of the different ways that regulation can support good research and good information for clinicians. I am not saying there is a direct parallel to this situation, but it may help understand the kind of challenges facing DA as it thinks about the right balance to strike.

I will reemphasize Dr. Shuren's point that there have not been decisions made in this area, and we are very much interested in hearing from a wide variety of perspectives. We will be thinking creatively. We really do want to foster innovation in testing, at the same time have high quality and high quality data to help patients and doctors.

So with that, I will just say good luck, and I hope it is a very productive and helpful meeting.

DR. GUTIERREZ: So good morning. I am Alberto Gutierrez. I am the Office Director for the Office of In Vitro Diagnostics.

What we will have now is we will have three talks

from the FDA, and the first one will be given by Courtney Harper. She is the Division Director for the Division of Chemistry and Toxicology.

DR. HARPER: Thank you, Alberto. As Alberto said, my name is Courtney Harper, and I am the Director of the Division of Chemistry and Toxicology Devices at the FDA, and I am going to be talking to you this morning about FDA's history with lab developed tests.

The purpose of this is to give you a little bit of a background and some context for FDA's thinking over the past 30 years as we have regulated other types of medical devices.

After my talk, Katherine Serrano will be giving a brief overview of the way that FDA currently regulates in vitro diagnostic tests, and following that Elizabeth Mansfield will start off the afternoon sessions today with giving the context for the questions that FDA hopes to answer and the reasons that we are here.

So first I would like to give a little bit of a context to the way that FDA started regulating medical devices. So as you know, the FDA has been in existence for over 100 years, but we actually didn't get the authority to regulate medical devices until 1976, and although a few medical devices were regulated before

then, the vast majority had not been.

In 1976, Congress amended the Federal Food, Drug, and Cosmetic Act to include oversight of medical devices, and the amendments to that law provided for a legal definition of medical devices.

Following that, FDA instituted regulations that actually specifically also defined in vitro diagnostic devices, and Katherine Serrano will go into that a little bit more and tell you a little bit about how FDA defines in vitro diagnostic tests.

These amendments to the Federal Food, Drug, and Cosmetic Act provided for risk- based regulation of medical devices, and part of the reason for that is that the scope of medical devices that are used for patient care is actually quite broad.

You have anything from a tongue depressor to an MRI machine, to a cardiac implant, and all of those types of devices needed to be reasonably regulated under this new legal framework.

So this risk-based regulation was brought into play, so that the level of regulation or the level of scrutiny that FDA might put on a knee implant is not equal to the level of regulation or scrutiny or the bar that is put up for something like a toothbrush or a tongue depressor.

The other thing that was needed is that the regulatory framework needed to have some built-in flexibility, because medical device manufacturers represent a broad range of different types of manufacturers, different types of facilities, and different types of products.

So the legal framework for regulation of medical devices was put in place so that small manufacturers and large manufacturers could operate equally under that framework.

So when FDA started this process in 1976, it actually took quite a while to basically get up to speed and start the way we are regulating medical devices today.

So first FDA actually had to create regulations or a regulatory framework for a lot of different aspects of patient protection for medical devices. We had to put in regulations for patient protection when medical devices are being studied.

We had to put in a framework for how FDA would, in a risk-based manner, evaluate certain medical devices before they went on the market to make sure they were safe and effective, and we also had to put a framework in for how medical devices would be surveyed after they were on the market to make sure they continued to be safe and effective and so that patients weren't harmed.

Another thing that FDA had to do in the context of developing the medical device regulatory framework was create a classification. We had to determine what the risk level was for each type of device that was on the market at the time.

To do that, FDA actually enlisted the aid of expert panels in a lot of cases. So panels were convened from a series of experts in the field for particular device categories, and within those categories medical devices were placed into classifications based on the risk of the way they are used.

So some medical devices were considered to be low risk devices. Some were in sort of a moderate risk category, and others were considered high risk and might have a high impact on patient health, if they were to fail.

So in this manner, FDA determined how they would move forward for each of those devices and the regulatory bar that they would have to meet.

When all this was happening, it didn't happen overnight. When the medical device amendments went into play into 1976, it wasn't the next day that FDA started to apply a lot of those requirements on the medical device manufacturing community. It actually took several years to have all of the medical device manufacturers come into compliance with the

applicable regulations.

So this type of authority was phased in over time, so that manufacturers were aware of what FDA was planning to do. They were given time to comment on that plan, and they were then allowed time to come into compliance.

So that worked fairly well, and so this is how FDA has been working on medical devices, including in vitro diagnostic devices, for the last 30 years.

Now I would like to switch over to in vitro diagnostic devices in particular. As you all know, in the United States there is a bifurcated pathway for getting to the market currently for in vitro diagnostic tests.

The pathway I have listed under number 1 is what I will call the commercially distributed pathway. These are tests that are manufactured in the factory, and they are assembled there, and the manufacturer collects data on their performance and their safety and effectiveness; and where devices may be a moderator or a high risk, they may come into FDA for premarket review, and FDA will grant clearance or approval.

Once that clearance or approval is granted, then those tests kits may be mailed out to multiple labs, and laboratories can use them across the country, according to their

validated instructions for use, and they can be used to provide patient results.

That is what I am calling the commercially distributed test pathway. These are the types of in vitro diagnostics that FDA has been enforcing our laws and regulations over for the last 30 years.

The lab developed test pathway, however, has also been in existence. Lab developed tests we are defining as tests that are designed, manufactured, and used within a single laboratory. So the laboratory actually sources all the reagents, designs the methodology, and does all the validation and follows all applicable laboratory regulations. FDA applies what we call enforcement discretion, and so these tests do not currently come to FDA for clearance or approval prior to going to market, and then these tests are offered within that laboratory to help with patient care.

So I mentioned that the current pathway exists because of what is called enforcement discretion. So FDA applies enforcement discretion over laboratory developed tests currently.

What enforcement discretion means is that it is the case when FDA does not enforce some or all applicable regulations on certain categories of products. This enforcement

discretion is not a practice that is unique to lab developed tests.

There are other categories of medical products and other types of products that FDA may have the authority to regulate but chooses not to do so. This choice does not change the fact that the law applies to those products. It really just changes the practical application of those laws and regulations.

So why would FDA do this? There's many different reasons for this, but it is all based on a risk. So sometimes it arises out of historical reasons.

Sometimes it arises because of resource or our timing issues, but as FDA chooses to continue a practice of enforcement discretion, it will generally always be based on risk, that the risks of doing so don't outweigh the benefits of doing so. However, sometimes those risks profiles may change and, when they change, FDA may choose to change the practice of enforcement discretion where it makes sense.

When FDA chooses to do that, often this is done through public discussion and guidance from the FDA announcing the change in that type of practice.

So when we talk about the laboratory developed tests that were out there and being used when the practice of enforcement discretion began, we are talking about types of tests

that were generally very localized.

They were small volume tests, mostly non-commercial, and performed in hospital laboratories. They were often a little bit more simple than some of the tests that we have out there today, using well established methods, and often single signal tests. So they were quite distinct for what they were measuring.

Things like immunohistochemistry or radioimmunoassay, for example, were things that were often developed as laboratory developed tests 30 years ago.

Where you have laboratory developed tests, because these were often performed in hospital laboratories, you had a close clinician/patient/pathologist relationship where often you might have a scenario where a clinician was seeing a patient, and they really were trying to figure out what was going on with that patient and, really, how they should decide to manage that patient.

So that they would go down the hall to their pathologist, and they would work together to determine a diagnostic scheme and any applicable tests that might be necessary, and where those tests were not already available commercially or where the lab didn't have them in place, they

were obligated to develop them in-house to make sure that the patients had adequate care.

So lab developed tests often were developed to meet unmet needs or to diagnose rare diseases where there was no incentive for anyone to manufacture a commercial test.

These types of tests, if they used calculations, were often simple calculations, often using a calculator, and they were generally for diagnosis or monitoring, trying to figure out what was going on with the patient or how they were doing.

A key aspect of the way that lab developed testing was done was that these tests often required a lot of expertise and interpretation from the pathologist or the laboratory personnel who were running them for interpretation.

So things like karyotyping -- somebody really had to be trained. They were not terribly automated at the time, and they had to know what they were doing in order to adequately interpret those tests.

So how did lab developed testing evolve? Probably the discussion started in earnest, and it started to escalate in the 1990s. In part, this was spurred on by the research going on in the Human Genome project where several things came together.

First, the Human Genome project spurred the development of technologies for molecular diagnostic testing that hadn't been in existence before, and these technologies became a lot more practical and a lot more available. So clinical diagnostic testing for genetics became a lot more feasible for clinical laboratories.

Because these were emerging types of tests and these platforms often came out of the research, virtually all of the clinical genetic tests were lab developed tests at the time.

Because these laboratories needed to use reagents for these tests, and the manufacturers weren't yet creating in vitro diagnostic test kits for these types of molecular diagnostic tests, there was widespread use of research grade reagents and research grade instruments for use in the diagnostic testing at the time.

So these research grade reagents were not under a quality system for manufacturing, and they actually might vary between lots. So FDA became concerned that the quality of testing might not always be the same that the laboratory understands because of the reagents that they are getting.

Additionally, outside of FDA there were some calls for additional oversight of genetic testing and some concerns that

the tests being performed might not have adequate clinical validation or validity.

So there were some calls for increased oversight and some discussion that FDA should step in and regulate lab developed tests, and genetic tests in particular.

There were other points of view that basically said that the laboratories were regulated under the Clinical Laboratory Improvement Act, or CLIA, and that no additional FDA oversight was needed, and that oversight would hamper innovation and hamper the laboratories' ability to create new tests and to modify them over time.

In the context of these discussions, FDA was asked about their role in the oversight of laboratory developed testing, including genetic testing, and this was the point at which FDA released first written statements about the practice of enforcement discretion and FDA's authority over lab developed tests.

So out of these discussions, FDA held a public meeting and proposed, instead of regulating laboratory developed tests, that they would regulate the reagents used in those tests, or the ingredients, to ensure that the ingredients that laboratories were using to create laboratory developed tests were made under

a quality system and that the quality of those products was consistent over time.

FDA stated at the time that, by assuring the quality of the reagents, patients would be -- laboratory developed testing would be allowed to continue. These tests would be able to be developed in a laboratory without FDA oversight, but FDA would apply this oversight over the components of that test, so that the quality could be better assured.

So this was a deliberate effort to allow the practice of lab developed tests to continue with a little bit of increased oversight over parts of that testing.

Now in that discussion and in the response to the comments to the ASR regulations that were put into place, FDA stated that, if the risk profile were to change in the future for genetic tests and other lab developed tests, that FDA may reconsider the practice of enforcement discretion at a future date.

So following the promulgation of the ASR rule in the late Nineties, molecular diagnostic testing really took off, and molecular testing platforms were advancing at a very rapid rate, and the addition of the ability to do clinical multiplex testing was also coming about. By multiplex, I mean the ability to measure multiple signals, usually molecular diagnostic signals, in a single

sample.

So these tests became very easy for a laboratory to do by purchasing Analyte Specific Reagents and specific types of instrument platforms, but they actually became a little bit more difficult to validate in that the proper clinical and analytical validation of multiplex tests require a larger number of clinical samples.

So these tests became a little more risky in that the link of the multiplex testing to the diagnostic outcome that they were claiming became a little more tenuous in some cases.

At the same time, there were certain manufacturers who also began to introduce Analyte Specific Reagents or products labeled Analyte Specific Reagents to the market that had a slightly higher risk profile than the types of reagents that FDA had envisioned when the ASR rule was put into place.

In the context of these actions, there was continued discussion over whether oversight of genetic testing and other types of molecular diagnostic testing was sufficient, and in 2001 the health and Human Services Secretary's Advisory committee on Genetic Testing released their own recommendations on genetic testing oversight.

These recommendations recommended that FDA be involved in the premarket review of new genetic tests, regardless of how they are formulated and provided, meaning that would include laboratory developed tests.

So as the new millennium continued on, the ASR regulations began to be a little fuzzy, and manufacturers either deliberate or inadvertently were misinterpreting the regulations that were on the books and the intentions of FDA in 1997 when we put those regulations together.

So these manufacturers were putting together generally molecular diagnostic test kits, that many of them would be classified as Class 2 or Class 3 in vitro diagnostic tests. They were putting them together in kits, calling them an Analyte Specific Reagent, and putting them on the market as exempt from FDA premarket review.

FDA thought that there was a risk to patients in this practice, because at that point neither the manufacturer nor the laboratory was able to sufficiently take responsibility for the quality and validation of the way that that test was put together and the way that it was validated.

So we decided we needed to clarify the intent of the ASR regulations, and in 2007 we finalized an Analyte Specific

Reagent question and answer guidance. This guidance was intended to clarify the boundaries of what was an Analyte Specific Reagent and the responsibility of ASR manufacturers.

This guidance document was published and final, as I said, in 2007, and a year later FDA began to be sure that the manufacturers had come into compliance, and started enforcing the law as explained by that regulation.

The enforcement of the ASR regulations actually created a little bit of an unintended consequence in that the ASR regulations were into put in place to prevent, in part, the practice of using research grade reagents for laboratory developed tests.

Yet when FDA started enforcing the ASR regulations, many companies, instead of coming in to get clearance or approval for the kits that they had been selling as ASRs, chose to re-label those products as "For Research Use Only," yet continue to sell them to clinical laboratories for clinical diagnostic testing.

So FDA found ourselves in the position of being in the exact same spot we were in, in the early Nineties, with regard to concerns over the quality of the reagents and tests for certain types of molecular diagnostic testing right now.

At the same time, there were other types of

activities going on that FDA began to be concerned about. Lab developed tests were moving away, like I said, from sort of single signals, more simple tests, into a realm of, in some cases, really high density testing or testing where multiple signals were being statistically correlated into a non-transparent result.

So FDA decided that this category of tests that were often offered as laboratory developed tests instituted an increased risk to the patients that they were being used on, because there was no independent review of the data in claims, and those data in claims could not be adequately evaluated by the physicians who use them.

We call these types of tests in vitro diagnostic multivariate index assays. Most IVDMIAs at the time were actually claiming very high risk intended uses. So sometimes they were for prediction of cancer risk or for prediction of which types of drugs cancer patients would respond to, Alzheimer's disease risk, risk of stroke, etcetera. So these weren't low risk claims.

Although these tests had intended uses that were quite useful, there was no assurance that the data supporting the test performance was adequate.

So FDA put out a draft guidance document stating that IVDMIAs posed an increased risk to patients and were unlike

traditional developed tests, and that FDA intended to require premarket clearance or approval requirements and postmarket surveillance and reporting requirements on tests that were IVDMIAs, even if they were offered as laboratory developed tests.

So this was FDA's attempt to sort of carve out a high risk area, but to allow the continued enforcement discretion for the rest of lab developed testing that weren't this type of high risk tests.

Publication of the IVDMIA guidance in the first draft and then subsequently in a following draft created a lot of controversy, and FDA got a lot of public input on the concerns and the fears and, in some cases, the support of the community on FDA regulation in this area. But there was a lot of questions and angst about FDA moving into the regulation of lab developed testing and, in particular, the predictability of only having certain types of tests regulated, while others aren't. How would I know if I have an IVDMIA versus how would I know if I had some other type of test?

In addition, there was another facet going on, and sometimes combined with the IVDMIA issue, where genetic tests began to be directly offered to consumers. So some companies were creating genetic tests, and they were allowing -- they were

mailing out sample collection kits directly to consumers without a prescription, and they were receiving those tests. They were performing genetic tests on them, and sending results back to the consumer.

This really began to come about in 2005 and in 2006, and it created some concern in the community. The Government Accountability Office initiated an investigation of Direct to Consumer tests for nutrigenetic testing, and there was a hearing in the Senate Committee for Aging in 2006 on this topic.

At the same time, FDA, CDC, and FTC got together and created a public service announcement, sort of a "buyer beware" article on genetic testing. The statements in that article said that the clinical validity of many of the claims made by these types of tests was unknown and that buyers should be skeptical of some of the conclusions that were given.

Some of these nutrigenetic tests, after the scrutiny that they fell under in 2006, began to be -- Some of them came off the market. Some of them ceased the Direct to Consumer testing model, but the Direct to Consumer testing model in general did not go away. In fact, in starting in 2007 and into 2008, companies began to offer Direct to Consumer genetic tests that were for more sort of high risk clinical claims.

So these tests purported to predict a person's risks or relative risks for certain clinical diseases, and this particular type of testing, I think, concerned the genetic testing community much more than the previous genetic tests that had been offered to consumers.

So the controversy and the public discussion escalated, and it is still, in fact, going on today.

So that brings us to today and when we talk about lab developed tests now, because really, the types of tests that were offered 30 years ago continue to be offered today in many cases.

So there is still a lot of testing out there that requires expert pathologist interpretation, that are single signal tests, and that are really performed because there is an unmet need, and there is a need for somebody to develop a test for a rare disease patient population.

So this continues and is a really important aspect of laboratories and laboratory developed tests. However, there has been a change in the way that laboratory developed testing is in the United States since 30 years ago when enforcement discretion began.

The volume and types of laboratory developed

tests have grown exponentially. So on the market today, you all know that diagnostic testing in general has exploded. Laboratory developed tests, especially in the last 10 years, 10 to 15 years, has really grown exponentially.

So the number of lab developed tests on the market is much, much, much greater than it was 30 years ago.

Today it is often used as a mechanism for the market entry for novel tests. So a lot of groups see lab developed testing as a way to get new tests on the market with sort of a lower bar, and so they are offered to patients at an earlier stage than they might be, should they need to have scrutiny of the clinical data behind those tests.

Today there is a higher proportion of laboratory developed tests in commercial labs and also as biological technology companies who are setting themselves up as laboratories, and this wasn't as evident 30 years ago.

So because of that, there is often little to no clinician/pathologist/patient relationship. So that relationship where a group of experts got together and created a diagnostic paradigm and a test intended to treat a single patient or group of patients now exists -- does not exist as frequently.

So tests are more often developed for broad

commercial use instead of use at a local facility. These tests are often really broadly advertised and aggressively marketed in some cases, sometimes advertised directly to consumers, and consumers are encouraged to go to their physician and order those types of tests.

Because of the advent and the advances in overnight shipping, samples can now be sent from Maine to be tested in California, and so Internet sales and nationwide and even international reach for testing is possible, where it was not possible before. So we have a case where it is no longer localized, but the patient population is a lot more distributed.

Lab developed tests today, especially the multivariate-type tests, now often require quite complex software, also for multiplex testing. This software can be difficult to develop, and it sometimes causes problems where patient results can be mismatched, if the software isn't created correctly.

Many incorporate automated interpretation more frequently than it used to be. So instead of that expert interpretation, now sometimes competent human intervention is removed from the equation for a lot of these types of lab developed tests. So this increases the risk in some cases and lowers it in others.

Tests are increasingly empirical and non-transparent. They often rely on complex statistical models and empirical links to datasets, but if they are validated incorrectly, the clinical validity of the test or the link of the test result to the way that it would be used on the patient is not always very well understood.

In addition, instead of tests being used primarily for diagnosis of a patient or monitoring for how they are doing, they are increasingly being used to predict drug response and also future risk of disease. So the risks involved in that type of test are somewhat different than the types of risks for the other types of diagnostic uses.

In addition, novel tests are often being developed outside of that laboratory and then being sold or "licensed" to a laboratory. So that the laboratory itself didn't actually develop the test in some cases. So it is more of a commercial model.

Currently, being a lab developed test is a self-designated term. So sometimes when a test is offered as a laboratory developed test, it may not actually be, technically, a lab developed test, and yet it is offered on the market as if the laboratory were involved from soup to nuts.

So a lot of times when people talk about

laboratory developed tests and the controls in place, they often refer to the Clinical Laboratory Improvement Amendment or CLIA, and a lot of people say, well, lab developed tests are regulated by CLIA, and FDA regulates the commercially distributed in vitro diagnostic tests.

We are very fortunate to have members from CMS here today and tomorrow who will be able to talk a little bit more about CMS's point of view, but I will just give a brief overview of the points of CLIA.

CLIA: The Amendments were put in place in 1988, and there was an effort to increase the quality of laboratory testing in the United States. So it put in place a certification process and accreditation requirements for laboratories, and it also provided for periodic inspections of the laboratory quality system.

It put in place education and training requirements for the personnel in the laboratories, and instituted proficiency testing requirements to make sure that the laboratory testing process was of high quality over time.

So the focus of CLIA is actually on the quality of the laboratory performing the test, but not on the tests themselves.

You also need to keep in mind that these Amendments were put in place in the context of existing FDA regulation of diagnostic testing. So CLIA regulation of labs is always intended to be complementary to FDA regulation of tests and not overlapping or contradictory.

There are some differences in the way that FDA and CMS handle laboratory testing. Both require registration and listing of some sort, where FDA requires that manufacturers register and list the tests that they provide. CMS requires that laboratories register and list the tests. Although currently not publicly available, they list with CMS.

Both have some requirements for analytical validation. FDA, for moderate and high risk tests, require that laboratory tests be analytically validated, and that data is reviewed prior to the time they go on the market to make sure that the test can accurately and reliably measure the analyte of interest.

CMS looks at analytical validity in a post hoc sampling apparatus in which they go in laboratory expressions, and they look at a sample of the tests offered by a laboratory after the test has already been put on the market.

There are no clinical validity requirements under CLIA, but for moderate and high risk tests FDA does review the

clinical validity data to assure that the device is safe and effective for its intended use.

Both CMS and FDA have a quality system. Both of them are assessed by inspection, but FDA adds onto that another feature called design control, which is the way that manufacturers monitor and ensure quality in the changes made to their devices, and all moderate and high risk devices and devices with software are required to have design controls.

Design controls are not required for laboratories under CLIA, and software is not at all addressed by CLIA.

The last point that is a little bit different is that FDA actually has a postmarket surveillance program. So that once a test is on the market, there are requirements for adverse event reporting and recalls of malfunctioning tests from the market. CMS does not have that aspect to their regulation of laboratories.

So what types of risks may this introduce, if laboratory developed testing continues under the current pathway? Clinical validation for laboratory developed tests is not required, as I have referred to already.

There is no independent review of data and claims before those tests go on the market. So nobody is looking

to see whether or not the company did a very good job or if the laboratory did a good job of demonstrating that their novel biomarker actually correlates with the disease they are claiming.

In addition, FDA has controls in place for the point at which the clinical validity of a test is still being studied. So where studies are still being done and the test is investigational, FDA requires that those be under informed consent and IRB approval as studies to study the clinical validity; whereas, often tests are released as laboratory developed tests while the clinical validity of that test is still being studied, and patients aren't always informed currently that the clinical validity isn't very well established.

There is no postmarketing and recall requirements for lab developed tests, and we have heard a lot of complaints that there is an unlevel playing field between the same test offered by a commercial manufacturer and a laboratory, that the laboratory has a lower bar for entering the market and can often undercut the costs of the commercial manufacturer.

We have also heard that there is a lack of clarity in what FDA will do and what CMS might do, and how this might move forward. This adds business risk and uncertainty for you all, and we all heard that particularly in the discussions around the

IVDMIA guidance.

So the risks of something going wrong with a test are going to be explained in a little bit more detail by Katherine Serrano and Liz Mansfield, but in a nutshell, we have actually had some interactions with some laboratory developed tests over the past several years.

In many cases, we have observed some things that are troubling. While there is a lot of really high quality laboratory developed tests out there, there are some tests that have had some significant problems.

These have included faulty data analysis, exaggerated clinical claims, fraudulent data, lack of traceability or change controls -- so where a change was made in a test, and it actually messed up testing a little bit so that incorrect patient results were reported -- poor clinical study design, and unacceptable clinical performance.

These are real examples, and all of these instances can lead to incorrect diagnosis or delay in diagnosis, and may, depending on the use of the test, actually lead to serious injury or even death.

So what is the current landscape? After the Secretary's Advisory Committee on Genetic Testing was disbanded,

a new advisory committee was formed call the Secretary's Advisory Committee for Genetic Health in Society.

In 2008, this committee provided recommendations to the Department of Health and Human Services on genetic testing oversight, and there was one recommendation that included a recommendation that FDA address all laboratory tests using a risk based approach.

This is notable, in that they actually did not restrict their recommendation to genetic testing. They felt like there was no difference, necessarily, in the risk between the genetic tests and another lab developed test, but that increased oversight in this area may be necessary.

Other government agencies have also studied this. In 2010 AHRQ finalized a Technology Assessment on the Quality, Regulation and Clinical Utilities of Laboratory Developed Tests, and there has been significance Congressional interest over the last five years or so on genetic testing oversight and laboratory developed testing oversight, in personalized medicine and in direct consumer genetic testing.

In addition, there is a change in the last 10 years or so toward personalized medicine. So I think all of us in this room are very interested in the advancement of personalized

medicine, and we all understand that diagnostic testing is going to be key in the advancement of this particular field.

So because of this, in part, there has been a vast increase in the use of diagnostic testing in clinical care. So this is great for the laboratory community and, we believe, great for patients, but it does provide a larger importance in some cases on the tests themselves and how they perform.

Also companion diagnostics, or diagnostics intended to be used to direct drug therapy, are increasingly being developed, and they may also pose different risks because of the decision of what drug to use or what drug not to use, are involved.

Today there are new business models than there were, different than there were 30 years ago. Whereas, 30 years ago if the pathologist down the hall wanted to develop a test, that was sort of their choice, companies are now being developed who are now seeing the lab developed testing pathway as an easier route to market to avoid FDA regulation of their tests. This is a little bit different than having a hospital laboratory develop a test.

In addition, this is being a little influenced because the lower regulatory risk involved in that pathway has been driving venture capital funding decisions.

We at FDA have also been hearing a lot from the

public over the last several years. Currently, we have in front of us a petition from Genentech asking that FDA apply an equal regulatory bar to all diagnostic tests, regardless of their place of manufacture.

Laboratory and manufacturer groups have proposed alternatives to traditional FDA regulation for tests, so that both laboratory developed tests and commercially distributed tests may be adequately addressed.

We are very lucky to have all of these groups here over the next two days, and we really hope to hear from them about their proposals and their suggestions for how FDA might move forward in reasonable oversight in this area.

We have also noticed that in the past five years or so, because of the increased discussion around the IVDMIA guidance and direct to Consumer genetic testing, there has been a little bit of a movement in some of the groups in terms of their thinking.

Whereas, before there were a lot of groups saying, you know what? FDA should stay out, CLIA is enough, with some of the high risk tests that have entered the market, we have actually started to hear a little bit of a change in that some groups have modified their thinking to think that, you know, it might be

reasonable now to consider FDA oversight of the higher risk tests.

So that brings me to today and why we are here. I want to emphasize that FDA believes, and has always believed, that laboratory developed testing is an important part of patient care, and that these tests are largely beneficial to patients.

So we recognize the importance of these types of tests and the need to have them continue to be available, but the discussion around FDA oversight of lab developed tests doesn't come out of the blue. Hopefully, my talk has given you a little bit of a context on the length of this discussion and on the evolution of this particular field and area.

This has been under discussion for over 20 years: Is there enough oversight over lab developed testing and genetic testing? FDA actually recognized the need for change several years ago, and signaled that in the Nineties with a slight increase in the regulation of lab developed testing components, and in the mid-2000's with the release of the IVDMIA draft guidance, signaling that there seemed to be some tests for which enforcement discretion may no longer make sense.

What we did hear loud and clear is that you all need predictability and transparency, and so this piecemeal approach of sort of going after chunks of tests in a way that needs

sort of an interpretation that may not be that clear is not a very good way to go, and it causes a lot of angst and a lot of issues for getting funding, for planning, etcetera.

So we are here today to hear about your suggestions for moving forward, so that we can come forward to discuss with you a more clear and comprehensive policy that may address the risk today, because what we are here to discuss today isn't necessarily what happened in the past and what happened 30 years ago, but it is really what makes sense now. What makes sense in 2010 for laboratory developed tests and the current situation?

So we really look forward to hearing your insights over the next few days, and we hope to hear a lot of really good ideas, and start a really good discussion on this topic.

So with that, I am going to close the sort of historical perspective, and it is my pleasure to introduce Katherine Serrano. She is from the Office of In Vitro Diagnostic Devices, and she is planning to give a little bit of an overview of FDA regulation of in vitro diagnostic tests.

We realize that some of you may not be familiar with the way that we currently work. So we hope that some information in this area may give context to some of the

discussions over the next couple of days.

So it is my pleasure to introduce Katherine. Thank you.

MS. SERRANO: Good morning. Actually, before I get started, I did want to mention, because we are not taking questions on the talks this morning, we have placed comment cards out by the registration desk. So if you have questions or comments, that would be a good way to communicate them to the FDA, and we will be reviewing those throughout the meeting today.

So as Courtney mentioned, I just wanted to provide a very broad overview of the FDA's current regulations for in vitro diagnostic tests. I will provide a really brief introduction to the FDA and IVD regulation, including talking a little bit about how we go about classifying devices currently, some of our pre- and postmarket requirements, as well as share some information and resources that the FDA has made available to manufacturers currently to help them navigate through the regulatory process.

So the legal basis for FDA's regulation of diagnostic tests comes from the series of laws that have been passed, and I have mentioned them on the slide here. I am not going to talk about all of them, but I will just focus on sort of the

two most important probably, the first being the Federal Food, Drug, and Cosmetic Act of 1938. We refer to it as The Act.

That is really the basis for most of our laws and regulations, although as Courtney mentioned, in 1976 medical devices were specifically called out in the medical Device Amendments.

At that time, medical devices were defined specifically as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or similar related article...intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of diseases in man or other animals." So a very broad definition.

From that definition, IVDs were further defined in regulations as "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including those to mitigate, treat, or prevent disease or its sequelae."

I think what is most important about this definition is that you can tell that it is very broad and encompasses may different types of in vitro diagnostic devices, not only those that do diagnose, but also those that predict risk as well as provide information on prognosis.

IVD classification, as Courtney mentioned, is risk

based. When we talk about the risk of an in vitro diagnostic, we really do so in the context of its intended use.

So the intended use is a specific statement that is made about the device that describes the general disease or condition that the device will diagnose, treat, prevent, cure or mitigate. It clearly defines the patient population that should be using that diagnostic, as well as the specific specimen type that should be used.

What is important about this is that a single in vitro diagnostic that can detect a specific analyte can actually have multiple intended uses.

So I have given an example here of an intended use for a pregnancy test, and you can see it is quite explicit. It for the "qualitative determination of hCG in urine for the early detection of pregnancy." This intended use statement also does specify that the device is meant for professional use.

Now what is interesting about hCG detection, of course, is that this -- in this case, it is being used for the early detection of pregnancy, which we would consider to be a moderate Class II intended use, although hCG could also be used to detect or to predict risk of developing cancer which, of course, would be a higher risk intended use. So, really, the intended use

does have to describe specifically in which patient population it will be used and for what purpose.

So again, when we think about the risk in the context of the intended use, we think about it in terms of what the consequence would be, should the test perform inadequately.

We have three classification levels, Class I being the lowest risk devices, and Class III representing those devices that could pose the most risk for public health.

Now before I get into the details of each different classification type, I just wanted to give you a broad overview of the different types of in vitro diagnostics that we have, broken out by device class.

As you can see, actually, most in vitro diagnostics are Class I devices. In fact, 50 percent are. Forty-two percent are Class II, so moderate risk devices, and only a minority eight percent actually represent the highest risk devices, Class III.

So Class I, as I mentioned, represent the most common, lowest risk devices, and some examples of these types of devices are actually lactic acid tests, erythrocyte sedimentation rate test, and differential culture media.

Now most of these Class I products are actually exempt from any kind of premarket submission, which is

important, especially when you consider that 50 percent of the devices that are the in vitro diagnostics that we regulate are actually considered to be Class I. So 50 percent don't have to come in and don't have to submit anything to the FDA prior to offering the test.

Now Class I devices are subject to something that we call general controls, which are essentially the basic requirements that are required for all medical devices.

Some of these general controls, as Courtney mentioned, do include registration and listing. So a medical device manufacturer has to register their manufacturing facility with the FDA every year, and at the time of that registration list the different devices that they manufacture.

They are subject to good manufacturing practices, which we have defined in our quality system regulation, which is 21 CFR Part 820. There are reporting requirements for adverse events and for recalls, should they occur, as well as there are provisions in these general controls for certain labeling requirements. Specifically, we would be looking to see that no false or misleading claims are made about the device.

Finally, there are some requirements for maintenance of records and certain reports that would need to be

sent to the FDA at various time periods.

Now Class II in vitro diagnostic devices do represent a slightly higher risk than Class I, and some examples of these might be factor deficiency tests, antimicrobial susceptibility test systems, or thyroid stimulating hormone test systems.

Unlike Class I, these do -- Most of these devices do require some kind of premarket notification, which we call a 510(k), that has to be submitted to the FDA prior to marketing.

There are also certain special controls that are applicable to these devices, and just like Class I, Class II devices also do need to meet the general controls that I just spoke of.

So the premarket notification is the submission that most Class II devices do need to make prior to marketing their device, and the submission for this has a 90-day review clock.

When the FDA reviews these applications, what we are looking for is really something called "substantial equivalence," which is basically showing that the new device is substantially equivalent to a legally marketed device or what we call a predicate.

What we mean by substantial equivalence in this context is really that the new device has a similar intended use and similar performance characteristics in the population that it is

seeking to address.

Now what it doesn't necessarily mean is that it has to have identical technology or be the same type of test offered. So, really, what we are doing with the 510(k) regulation is leveraging some of the information that we know about a device in that similar intended use population for offering the test for a certain reason with this new technology.

Now while some submissions do require clinical data, actually the majority of these 510(k) submissions do not have any clinical data, and we try to be as transparent as possible and post information about our review of these applications as well as a summary of the types of information that were submitted to us on our website.

As I mentioned, Class II devices actually do have special controls in addition to the general controls. What these are, are additional requirements for when the general controls alone may not be sufficient to adequately assure safety and effectiveness.

So some of these special controls could include certain labeling requirements, mandatory performance standards, or even postmarket surveillance requirements to more adequately assure safety and effectiveness.

When special controls are in place, these are described through guidance on our FDA website.

Now Class III devices, obviously, represent the highest risk, most complex devices, and also include those devices for which there is no legally marketed predicate, so anything that is really novel or has a new intended use.

Some examples of this include Hepatitis B and C testing, HPV tests, total PSA for prostate cancer screening, as well as Continuous Glucose Monitoring Devices.

Like Class II, these products do require a premarket notification to the FDA, or a submission being sent to FDA prior to marketing, but the regulatory bar is a little bit higher, and actually the submission in this case is called the Premarket Application or a PMA.

Because these submissions tend to be a little bit more complex, a lot of these do come in with clinical data as well.

So as I mentioned, the review of this application is a little bit more involved, and we do have a 180-day review clock. Unlike the Class II products, PMA devices do not actually compare themselves to a predicate, but instead they actually have to show safety and effectiveness of their device.

Unlike Class II devices, there is a FDA inspection

performed of the manufacturing facility prior to approval, and in some cases the FDA does seek Advisory Panel input prior to approval.

Again, in an effort to maintain transparency, we do post a summary of the safety and effectiveness data, which is a summary of the data that was presented to us in the PMA, as well as some of our review criteria on our website.

Now as I mentioned, Class III devices do include those devices for which there is no legally marketed predicate. So anything new is, automatically by default, a Class III, and it is sort of a quirk of the law, because in some cases certain new devices might not pose the same amount of risk as a Class III device.

So in the 1997 device amendments, we tried to sort of get around this quirk of the law by creating what is now known as the de novo process.

Really, the de novo process is specifically for these devices that might be new, have a novel intended use, so they can't come in under the 510(k) program but don't represent the same amount of risk as other Class III devices. The risks that they do pose could actually be mitigated through special controls.

So this de novo process is actually used as a

mechanism to down-classify devices that would otherwise be automatically Class III, and in that down-classification special controls are actually implemented for these novel devices.

The classification for that novel device is published and, in effect, it becomes a predicate for a future device that would come in with the same intended use.

This has actually been a really great process, particularly for novel in vitro diagnostic devices. It is very well utilized in our office.

Now something that is not necessarily tied to device class but I did want to mention were actually investigational status devices. In the case of IVDs, actually, most investigations are actually exempt from any kind of premarket requirements, any information needing to be sent to the FDA, particularly if the test doesn't actually introduce energy into the subject, if test results are not returned to the patient or to the physician, and if no invasive measures are needed to actually obtain the sample.

So if, for example, a biopsy was going to be taken for another purpose and that sample was used for this IVD investigation that would be considered to be an exempt investigation, although, obviously, if the biopsy was going to be obtained just for the purpose of the investigation, then it would

not be exempt.

So in the case of a non-exempt device, submission is required, and the review clock on that is 30 days. So it is a pretty quick turnaround, but really, there are some rules in place for these investigational devices that are really meant to protect patients, including things like the device needs to be labeled for investigational use. Informed consent, obviously, needs to be obtained to get the samples, and IRB approval is required of the study.

So now for both 510(k) as well as premarket applications, there are certain requirements that we look at premarket in our review of these new devices.

For all IVDs, for example, we do look for them to establish analytical and clinical validity. So in terms of analytical validity, what we are looking for here is information on how accurately the test measures an analyte, as well as how reliably.

In terms of clinical performance, we are looking to see how reliably the test can actually measure the clinical condition that it is claiming.

We also do a review of the labeling to ensure that there are adequate instructions for use, that appropriate warnings or limitations of the diagnostics are communicated to the user, as

well as information on how to interpret the test, and a summary of the device's performance are included as well.

Now in terms of analytical performance, there are many characteristics that we look for, and I will just mention two. When we perform our reviews, we are looking to see that manufacturers have followed such protocols such as CLSI in the evaluation of their device performance.

So we will look at aspects such as repeatability, reproducibility or precision, accuracy and "truth," the comparison could actually be made to a reference method or the predicate device that a new device is claiming substantial equivalence to or, in some cases, the clinical endpoint.

We look to see that Limit of Detection/Limit of Quantitation is defined, that studies are run in the linearity or to characterize any interferences or cross-reactivity that might occur with that diagnostic.

We look for studies that analyze cross-contamination/carry-over and matrix effects, etcetera.

Now in terms of clinical performance, we do look for clinical validity. So the device actually has to have a clinical indication. Typically, that clinical indication should actually add value to clinical management.

Now these validity claims can be based on many different types of information. In some cases, actually no clinical data needs to be submitted to us at all. So, for example, in the case of sodium, it is pretty well understood. No clinical data would actually be required.

In some cases, new clinical data is required. In many cases, we see literature being used to support validity claims, as well as current clinical practice guidelines.

So when clinical performance is demonstrated in a premarket application, a lot of times we do see that retrospective studies are being used. I think a lot of people don't necessarily know that. I think they see the FDA, and they automatically assume that we are only looking for randomized controlled trials, and that is actually not the case.

Most of the studies that we do see are retrospective, and that is fine as long as the study does support the intended use of the test. We look to see that samples are collected and stored appropriately, and in a manner that reflects current practice, and that there aren't sampling biases to be concerned about.

We also see that a lot of literature is being used to support devices, and again that works very well, as long as the

studies that are being used are analyzed and applicable to the device claims.

Now in the event that a new study is actually needed, the study needs to be designed in a way that it reflects the intended use population.

In an ideal situation, obviously, samples would be prospectively collected, although we often see retrospective samples being used. The study needs clearly define inclusion/exclusion criteria and have a robust statistical design.

When these new clinical studies are reviewed, we do use a team of experts, including statisticians, clinicians, subject matter experts. In some cases, we will actually hold Advisory Panels to analyze the data, and we often use clinical practice and society guidelines in our decision making process.

As Courtney mentioned, we do actually perform software review and instrumentation review on all diagnostic devices, as all software and instrumentation used in diagnostic test systems are regulated by the FDA.

What we are looking for here is total system validation. I won't get into too many of the details of how to do this, but I will just refer you to our website where there is a lot of information on the types of information that FDA is looking for, for

software and instrumentation validation.

Now from a postmarket perspective, there are also requirements, including those related to current good manufacturing practices or, as we call it, the Quality System Regulation. This regulation is outlined in 21 CFR Part 820.

Now this regulation requires that manufacturers have an appropriate quality system for their manufacturing operation, and I really emphasize the word appropriate there, because this regulation was actually written to be flexible.

It is meant to encompass both the small mom and pop manufacturing operation that may only have one or two employees, all the way up through the giant multi-national corporations.

The point here is that the same quality system -- we don't expect to see the same type of quality system with the same quality elements from the mom and pop level, mom and pop shop level, all the way up to the multi-national. It should only be what is needed to assure quality in the design and manufacturing.

So some of the elements that this regulation stipulates are for trained personnel to be involved in the design and manufacture of these devices, and that those facilities be appropriate for the manufacturing operations that are performed

there.

Again, the device design process needs to be controlled. The manufacturing process, packaging, labeling, storage of devices -- that all needs to be controlled. Purchasing of different components has to be adequately controlled, etcetera.

There needs to be a good system, in place to both identify and correct as well as prevent problems that could occur. There are stipulations for specific complaint handling procedures, and certain documentation requirements.

Now as I mentioned with the general controls, there are requirements for all medical device to report adverse events or even deaths that have occurred in relationship to the use of their device.

The other thing is sometimes, if the device malfunctions and it could have caused death or a serious injury, but it doesn't actually, those types of events are also required to be reported to the FDA.

There are various time frames for these reports, but once the FDA does receive these reports, we will analyze them to determine whether further action is needed.

Now we also oversee recalls, and recalls are the method of removing or correcting products that are already out in

the field that are otherwise defective. These products typically represent some kind of risk of injury or gross deception or are otherwise defective.

Most recalls are actually voluntary by the manufacturer, but these are required to be reported to the FDA. Once they are reported to us, we do an analysis. We classify the recall, and we communicate information to the public on our website, as well as we do try to oversee the actions that the manufacturer takes for the recall to ensure that they are adequate.

Now I haven't given a lot of information on enforcement, FDA enforcement, but I will just say that we do have many tools available in the event that there are violations or activities going on.

One way that we enforce our regulations is actually carrying our periodic inspections, and then we have a number of tools, as I mentioned, in the unfortunate case where there are violations of the regulations.

Now we have -- We do recognize that our regulations are complex and that they are very involved, and so we do try to have a lot of information available to manufacturers to help them navigate through this process.

Probably, I think, the best way and the way that I always recommend people to get information from the FDA on specific issues is through something called the preIDE meeting.

These meetings -- I would say that the title of these meetings are a little disingenuous, because they don't need to actually be tied to an IDE submission specifically, but actually can be any kind of presubmission type meeting.

So if a sponsor has a specific question and they want to get the FDA's feedback prior to sending in a formalized submission, this is a really great tool to do this. It is meant to be a flexible process.

So if there is any information that the sponsor would like from the FDA, it can be requested. These meetings are not binding either on the part of the FDA or on the sponsor, and can be used to help sponsors with any number of issues, such as perhaps refining an intended use statement for their device, designing appropriate validation plans or clinical studies, etcetera.

I would say that these are particularly useful for perhaps a sponsor that is not as familiar with the FDA and might be new to this area of regulation or, if there is a test that somehow is very unique and different that the FDA might not have seen before, it can be helpful to start a dialogue to let both the FDA as

well as the manufacturer begin to understand what kinds of requirements would be needed for future submissions.

The FDA also participates in a number of outreach activities every year. One such outreach activity is the 510(k) workshop which our office, the Office of In Vitro Diagnostics, does participate in yearly.

This workshop is put on to really help provide education on submission requirements as well as strategies for more effective submissions. What is great about this workshop, particularly, is that a lot of the informational sessions are actually led by FDA reviewers. So these are the people that do the reviews. They know what kinds of information they would like to look at. They know what kinds of information they would be asking for.

So we usually find that there is a lot of very good communication that goes on in these workshops, among the manufacturing regulatory as well as the FDA sort of Federal perspective.

The FDA also does participate in a lot of workshops and conferences. We give lots of outreach talks at the various medical and device society meetings throughout the year. And of course, if there is a need for additional education and

outreach workshops, we do those on an as needed basis.

Now most medical devices are actually manufactured by small corporations. So to help that community specifically with specific helping them navigate through the regulatory process from the perspective of being a small manufacturer, we actually do have the Division of Small Manufacturers, International and Consumer Assistance, or we call them DSMICA, and they are set up to specifically provide assistance and guidance on pre- and postmarket issues with this perspective of the small manufacturer in mind.

As I have mentioned, with the premarket applications there are a lot of ways to get information on the way that we review both 510(k) as well as PMA products, and those -- because we do post our decision summaries of safety and effectiveness information on the web.

For de novo products, we also post the special controls guidance documents on our website. It is a little confusing to get to these, to get to, particularly, the review summary. So I just want to provide these slides here so that later, if people want to look at them, they can figure out how to get to these decision summaries.

Basically, what you have to do is you have to go to

the 510(k) database, which I have listed here, and perform a search. You can do the search based on the manufacturer, based on the device name or a product type.

Once you pull up the record, you will have to scroll down to the FDA review portion and actually click on the decision summary link.

This decision summary has a lot of really good information on it about devices that have recently been cleared, including some of the types of information that they have, some of the questions perhaps that the FDA posed.

This can be a really great tool, especially for somebody who is new to our regulations to see sort of a template on the types of information that they should be sending out, and perhaps the format for that information.

Now in a similar fashion, you can get this information about PMA products. You will have to go to the PMA database, perform the same type of search, and scroll down to information about, and actually click on the Summary of Safety and Effectiveness.

Again, there is information on the preclinical studies that were sent in, the clinical studies, any conclusions that were drawn. If a Panel meeting was needed to make a

determination on the approval of these products, their recommendations are posted there as well.

Another really great resource are Guidance Documents. These are formal documents that FDA publishes to provide information on our current thinking of a given topic.

Something that is really interesting about these is they actually are issued typically in draft form first, and that gives the opportunity to the public to comment on the document and provide perhaps some input on how it might be modified before it is published in its final form.

I have provided some examples just to give you a feel for what types of information we tend to publish in guidance.

Now our office, OIVD, does have a website where we try to compile a lot of the information that is specifically relevant to diagnostic devices, including information on our regulations, certain guidance documents that are specifically related to diagnostics, information on CLIA categorization, standards, and specific information that can be useful to lab and users.

Now for more general device information, the CDRH website also has a place called device advice, and this is a website that has a lot of information in general on medical device

guidance, regulations, databases and provides a lot of information on how to make submissions, some of the pre- and post-market requirements.

Well, I thank you very much for your attention today, and we really look forward to your comments at the rest of the meeting.

DR. GUTIERREZ: So we are running quite a bit early. So I propose what we do is we will take a break now for half an hour. Perhaps what we can do is -- What this will likely mean is that we will start the public presentations this morning instead of this afternoon, if the people are around, and maybe we can stretch actually the time that we have for the panels and for discussion, which actually would be good.

We only had given an hour. So perhaps we can make that a little bit longer. So how about if we are back by 9:50 for Liz Mansfield's presentation then.

(Whereupon, the forgoing matter went off the record at 9:19 a.m. and went back on the record at 9:52 a.m.)

DR. GUTIERREZ: So we are not quite as full as we thought we were going to be. So if there are people who are in the overflow room that actually want to come to the main room, I believe we have enough space. So they should do so, so they

can be part of the meeting, if they would like to.

Before we start, I was remiss at the beginning to actually introduce all the people that were at the table. Dr. Shuren, obviously, was introduced the meeting, but with us we also have Dr. Ginette Michaud. She is the Associate for medical Matters at the Office of Blood in CBER. She is with us, and Dr. Sally Hojvat, who is the Division Director for the Microbiology Group in the Office of In Vitro Diagnostics.

So now we are going to go through, and we are going to have Liz Mansfield give a talk, and then after this is done, we will start with the public comments. We will go through as many as those as we can get in before 11:30, and then we will take a break for lunch.

So the next talk then is going to be given by Dr. Liz Mansfield. She is the Director of the Personalized medicine program in the Office of In Vitro Diagnostics.

DR. MANSFIELD: Well, thank you all so much for coming to see us today. I am impressed and somewhat staggered by the number of people here.

So I am going to talk a little bit about FDA's considerations and what we might do concerning the talks you heard previously and implementing some sort of oversight of

laboratory developed tests.

So much of what I say, you will have heard before. So I am perhaps jut reemphasizing it. Why are we here today? I don't think anybody would argue that we are in a new era of molecular diagnostics and personalized medicine.

I also think that there is broad agreement that diagnostics are the linchpin of personalized care, which is where our health care system would like to be heading, I think.

We feel very strongly, as do others that the public needs assurances that diagnostic devices are sound and reliable and the results that are delivered from them are actually accurate.

I will take a moment to remind you of FDA's mission, which is not a new mission, which is to promote the public health, which we certainly would like to do, but to protect the public health. We have got a dual mission.

We do that by weighing benefits and risks. Where we see the risks rising beyond the level that makes us comfortable, we feel obligated to take some action to protect the public health.

So let me start off. I think previous speakers made this point, but I will make it again, that we agree. LDTs provide value. Laboratories, who are often closer to the patients,

tend to be highly motivated to create new tests for unmet needs.

They often address smaller volume tests that wouldn't make it on a larger scale manufacturing platform. They are often offered so that they can be in geographic proximity to the patients and have a rapid turnaround time, which may not be true of other types of tests.

Labs may provide specialty tests that require specific technical expertise and training that would not translate easily in a commercially distributed IVD kit, and they can provide a rapid response to a critical need, as we saw in the recent H1N1 emergency use authorization.

At the same time, FDA oversight adds value. As the two previous speakers have very carefully outlined, I think we provide risk-based oversight of in vitro diagnostic devices by applying basic controls, independent premarket review, and postmarket monitoring of several types.

Our goal is to provide the public with reasonable assurances of predictable performance of these tests, uniform and properly controlled manufacture, as well as detection and correction of malfunctions and failures.

So what is happening now? I think all of you know, but I will tell you anyway, there is a bifurcated regulatory

strategy. Courtney demonstrated it in pictures on her slides. This bifurcation exists between what are called laboratory developed tests and what I will call commercially distributed IVDs.

As has been discussed before, laboratory developed tests have evolved in many ways to become a lot more like commercially distributed IVDs in terms of the business models used, the geographical outreach, and the ability to test multiple analytes from a single specimen.

So today, the logical basis of this bifurcation has faded somewhat. We also perceive and are told that there is uneven, unlevel playing field in the industry in which traditional manufacturers, who have a lot of experience in designing products, manufacturing products, and controlling them after they are on the market, feel that their ability to create high quality, innovative products is being stifled if, for example, a laboratory can rush to market without necessarily having all the same controls in place. So we worry a little bit about that. We want innovation from all sectors.

We also worry that laboratory developed could be introducing unreasonable risk to patient health through uncontrolled design and manufacture, unsupported claims, or claims that are preliminary, as well as unreported malfunctions

and failures of devices.

Some of these current issues have been touched on before, one of which is the status laboratory developed test or LDT is self-applied. No one from the FDA goes out and says you are a laboratory developed test. That is something that laboratories decide for themselves. There is no formal regulatory definition.

Many labs offer tests created by others, or substantially created by others, as laboratory developed tests, and thus are technically not subject to -- or are covered under the enforcement under the exercise of enforcement discretion by FDA. So we don't review them.

So we see LDT being more and more used as a loophole in many cases, as a way to go to market quickly without independent premarket oversight.

We are seeing a lot of preliminary information coming out of scientific studies and so on that are published in the literature that is being packaged for use as medically actionable information, and we think in many cases this is premature. There is not enough data to support the claims.

We know that formalized control of design of LDTs is often lacking, and design control is really the direct guide in

FDA regulation to what and how to validate in your test; and if you don't do design control, you may not go down the right validation path. And of course, software is uncontrolled, and software design and validation principles are critical to having good software.

So where are we today? We stand before you saying nothing is written in stone. We have not made any decisions, and that is completely true. I want to reassure you of that, but our considerations in being here with you today are: to provide an assurance that laboratory developed tests are safe and effective, while still facilitating innovation.

We are aware that there is a lot of anxiety over duplication or conflict with CLIA. We intend to avoid duplication and, if we can detect a conflict, work it out.

We are considering using CLIA or other deemed inspectors for our inspection processes. So that is area that you may already -- or you should already be familiar with, and certainly, our goal is to avoid disruption of critical testing.

So you have already seen twice risk-based classification, and I know this is an area of pain for many people who are not terribly familiar with FDA's processes. So I will go over it again in a slightly different way.

So classification, as has been mentioned before, is kind of based on how would an undetected false test result affect a patient or patient management? We have three classes, Class I, II and III, with Class III being the highest risk.

Class III devices often have a possibility of serious injury or death, if there is an undetected false result. It is often difficult with these types of tests, because they may be complex, to detect a false result, and many tests that hold a high public health risk, such as infectious diseases and so on, will be of high risk; because not detecting an incorrect result there can cause widespread public health issues.

A result -- A false result from this type of test could lead to incorrect and harmful clinical management. It could lead to an unnecessary invasive procedure. It could lead to a failure to follow up a serious disease.

So I am giving you here the way to think about classification, and some examples of this are companion diagnostics, tests for cancer diagnosis, tests that direct or very strongly influence management of serious disease, and certainly, tests for serious or fatal communicable diseases. Those would be considered, in general, high risk. This is, of course, all based on the claims you make for the test.

The moderate risk tests tend to have the potential for non-serious injury or injury that is medically manageable. They may have relatively easy to detect false results, and they may be adjunctive tests, tests that are used as one part of the totality of information for patient clinical management.

If test results are wrong here, you may have the potential for delayed test results, uncertain clinical management, because one test result doesn't fit with the others. You may have continued testing for the same reason, and an incorrect test result and many of the genetic tests that we have classified as Class II could lead to psychosocial issues where the family is disrupted by a result that they weren't expecting.

Some examples of these types of tests are tests like genetic tests where the phenotype is already known and you are confirming it genetically; tests where there are multiple findings used to direct clinical management, but where each finding has specific weight; and tests that are used to monitor already detected and diagnosed disease.

Our lowest risk tests, usually Class I, tend to have little potential for injury, if the test result is false. They often have -- False results are easy to detect. It is obvious that they are wrong, or they may be very highly adjunctive. It is a very small

piece of information used in the larger context.

False results from these types of tests, again, are unlikely to direct clinical management. They may provide some sort of medical knowledge only without a change in management, but knowledge that the physician considers to be important, or they may provide an evaluation without directed management. The physician takes everything in and says, practice of medicine, I am going to put it through my own algorithm in my own head and use it.

So among these are tests that identify one among many defining characteristics of, for example, a tissue or a cell -- does it express karatin? Does it express leukocyte antigen, something like that? -- tests that have little clinical impact but are still important, and certain instruments and equipment.

So what is our approach to all of this? You have heard that we have 30 years of history of worrying a little bit about lab developed tests, and so I wanted to give you an idea of an approach. Again, this is not confirmed. This is not finalized.

First, I want to start out by pointing out that FDA regulates tests. It does not regulate labs. That is CLIA's job. So we do hear a lot that FDA wants to regulate labs. In fact, we do not. We want to regulate tests.

We think FDA authority can address oversight in an even-handed way to benefit both labs and consumers. We do know that the problems that we see with laboratory developed tests, some of which have been mentioned before, are not applicable across the board. Not every lab has problems, but FDA oversight would bring value as a uniform system.

So if you have a lab, look at the person next to you and say, do I know that that person is doing everything that they should do? We need a way to actually see into this and evaluate these tests.

We are believing, as has worked for us for the past 30 years, that a risk-based framework might be appropriate for all manufacturers and add value in both laboratory developed tests as well as commercially distributed IVDs.

We have, of course, done some thinking prior to being here, and come up with some elements that we think might be helpful to think about, and we hope that we hear some comments from you today.

One of our issues will clearly be resource management within the FDA. Bringing laboratory developed tests under oversight will require additional activity from us. So we have considered a revisit of currently regulated tests to assess

potential for down-classification.

So there may be tests out there now that we are actively doing premarket review for. We may look at them and say that premarket review doesn't add much value, let's not do that; let's do some higher risk tests.

We would probably want to consider a phase-in over time based on risk to allow for predictability and planning from the laboratory community. So we might want to look at the highest risk tests first, and then over time bring in others.

We will probably need a list of who offers what. We don't know what the universe of LDTs is now. They are not registered and listed with us, and nobody has these records, or at least they are not telling us.

You are probably aware of NIH's Genetic Test Registry effort. We may be able to coordinate with them. They are asking for voluntary registration for genetic tests, although we may be able to expand that beyond tests. I don't know. At any rate, we will probably need to expand our registration and listing in order to encompass all the tests that are out there.

We will probably need to implement modifications to our current oversight structure, where we find that they are appropriate and within our laws and regulations.

So these are the kinds of things we hope that you will help us understand what some good approaches might be.

So how is FDA going to manage oversight of LDTs, assuming that we go forward with this model? Again, as I stated before, we will plan for some reassessment across the board. Our goal is to focus on risk, and we will adjust the oversight applied to all tests, if needed.

We will use and we will build our resources according to the need that we see, and we are able to track that very easily by how many submissions are coming in the door, how long it is taking to review them, and so on.

We may need a phase-in, as I mentioned. We may need some down-classification activities. We could look at pilots for third party accreditation of other bodies than FDA that might perform premarket review of, for example, some lower risk tests or something like that, and might act as inspectors, possibly even combining with CLIA so that we wouldn't disrupt laboratory time too greatly.

How will you all, the stakeholders, get information about what is going on, and how to do what FDA might ask you to do? We understand more than clearly that this process will require a tremendous amount of outreach and

education.

We would likely approach that through guidance documents that have been discussed before, the IVD Forum and other workshops that we already hold, the preIDE program where you can come into FDA and talk prior to making a premarket submission to make sure you have got everything sort of the way it needs to be.

We can hold informational meetings that we have not done a lot of in the past, but can do by going around the country and people can come and ask questions or we could have more structured meetings or whatever you want or need.

We can make use of our Advisory Panels, perhaps for classifications, new classifications or for distributing information. Certainly, I would want to encourage everybody who is considering coming to see us to ask direct questions to the FDA staff. We really are approachable. You won't always hear what you want to hear, but we are approachable.

So the framework for oversight of LDTs is still to be written. We have certain questions to be addressed, and these I have mentioned briefly previously in my talk.

We really need to know who is offering what. We need to understand what the appropriate risk stratification for

all IVDs is. Do we need to go back to Advisory Panels to readjust things, as was done in the late Seventies? And do we need to determine if there are tests and labs that can remain under enforcement discretion or some lower bar of regulation in order to keep needed products on the market, in order to make sure that the public health is served?

We may want to do, as I mentioned, phased-in timelines, both for review and compliance with the quality system. We don't know exactly what a reasonable phase-in would look like. We would love your advice on that.

We need to consider how much is this going to cost labs over what they are spending now, and how much of that can be mitigated, and how much of it is sort of some cost.

We need to worry about inspection, because we know labs are inspected already, usually by at least one body, CAP or CLIA, and if FDA adds onto that, that may be a burden to labs. Is there some way that we can handle inspection more efficiently? We don't know.

I will say again, there is no intention to disrupt critical testing here. So we will be working on ways to assure that the whole system doesn't shut down as we move forward.

I tried to talk as slowly as possible, but obviously,

it wasn't slow enough. So now I will return the podium to Alberto. Thank you.

DR. GUTIERREZ: So before we start the next session, actually, are there -- Does anybody have any questions for the previous FDA speakers, anything that they would like us to address?

AUDIENCE MEMBER: It is a quick question on the risk side that presented a risk stratification. Can the speaker clarify if the FDA knows yet whether the line it said about cancer diagnostics -- whether that would cover any test in the highest risk stratification category that relate to cancer, such as risk of recurrence, prognosis tests, or was that really just cancer diagnostics? Thank you.

DR. MANSFIELD: Let me see if I can run backwards here. Our current approach has been monitoring already diagnosed cancer and prognosis have not been considered high risk in the intended uses we have received.

I can't guarante that that would be 100 percent true, because everything depends on the claims you make. But currently, we have mostly been treating those as Class II.

AUDIENCE MEMBER: I was just curious. Why are companion diagnostics automatically Class III? What if they

are companion diagnostics were something other than a serious illness such as something that would -- something as simple as, let's say, a P450 test?

DR. MANSFIELD: Well, first of all, I didn't say anything was automatically classified as giving examples, and companion diagnostics, we think, will drive whether a drug is used properly or not, when that drug has been designed using the companion diagnostic.

So if that result is wrong and it is undetected, the patient may suffer harm. So I don't want to get into a long sort of regulatory discussion of this, but that is the general idea.

DR. BOLLAG: Good morning. Dan Bollag from ARIAD Pharmaceuticals. I just had one more question on one of your last couple of slides that you had.

You had a series of topics that you were interested in and an additional topic, I guess, that we are also interested in is if you are looking forward to changing the way that you apply your enforcement for laboratory developed tests, how will you manage those tests that are already out there, those, if you will, predicate tests, would be an interesting topic.

DR. MANSFIELD: I'm sorry. I didn't hear the last part. How will we manage the tests what ?

DR. BOLLAG: So if you are going to change your expectations, if you will, for laboratory developed tests, for tests that are currently already being offered as laboratory developed tests, how will you manage that cadre of tests?

DR. MANSFIELD: That is a good question. That is one that I didn't list here, but we don't know, and we would like input.

DR. DAVIS: Bruce Davis, Trillium Diagnostics. I have a question regarding the historical review earlier today. As somebody with enough gray hair to remember when the ASRs went into effect, it is my recollection that the prime motivator or drive behind that was really monoclonal antibodies, and that molecular diagnostics was kind of add-on later. Am I incorrect in this or is there some reason why we are ignoring monoclonal antibodies?

DR. GUTIERREZ: We can ask the author of the ASR later on. Steve Gutman is here. But having said that, I believe that, if you read the ASR rule, clearly, monoclonal antibodies were part of what was going on, but at that point so were genetic tests.

If you read, it actually points out. So I think it was both. It wasn't just one or the other.

MR. TERRY: I have a question on Dr. Mansfield's -- My name is Patrick Terry, Technic Solutions -- about the framework of a pathway forward. I was curious why the agency has not highlighted notice and comment rulemaking as a potential way forward. I would be curious to hear the agency's perspective on the flexibility of guidance, the constraints of notice and comment rulemaking, and what the decision process has been and so forth at the agency.

DR. MANSFIELD: So, Jeff, are you going to take this one?

DR. SHUREN: Sure. The reason why not for notice and comment rulemaking is because the requirements actually already apply now. The law is in effect. We have simply, as a matter of policy, determined not to exercise or not to enforce that authority as of right now.

So when we engage in enforcement discretion, either put it in place or take it back, that is a guidance process. It is a matter of policy. It is not imposing a new requirement. The requirements are already there.

MS. JAVITT: Hi. Gail Javitt, Sidley Austin and Johns Hopkins. I appreciate the point that FDA regulates tests, not laboratories, but unpacking that a little bit further: When

FDA regulates things, it also regulates the labeling about those things.

I am curious how you have started to think about what is and is not labeling when you are talking about a laboratory developed test?

DR. MANSFIELD: I was just going to say, you know, I think that is an issue that we need to work out based on our statute and regulations, what is and is not labeling, and I don't think I can give you an answer here today.

DR. LINDER: Mark Linder from University of Louisville and PGXL in Louisville.

It seems that the context of these discussions is as though it is a foregone conclusion that -- You know, FDA regulates tests, not labs, and it seems to be a foregone conclusion that you want to maintain that structure.

That seems a bit unclear to me. Maybe we can discuss or you can talk a little bit more about why, through CLSI or traditional regulation mechanisms to regulate laboratories, why that is maybe not the direction to be heading here.

There is a lot of very good clinical laboratory leadership out there. So I wonder why this is a foregone conclusion, that we shouldn't possibly be focusing more on the

structure or the laboratory and doing it through laboratory mechanisms rather than still trying to cross-walk here where you are doing tests but not labs. That seems that is always going to be a conflict. So I just wonder why that is a foregone conclusion.

DR. GUTIERREZ: I think -- I will take this one. It was clear in the talks, and I think we can put those slides up again, that there is definitely some gaps in the regulation. Probably the biggest gap of all is clinical validity, and all you have to do is go out there in the web and look, and you will see all kinds of tests that a lot of people will tell you are not very well -- the data doesn't support them very well.

So you can look for tests for autism. You can look for tests of all kinds of things that people claim out there. The CMS and CLIA doesn't look at clinical validity. All they make sure is that there is some form of medical validity at the laboratory. Nobody is actually looking at that. That is one of the gaps.

There are other gaps, and so the question is -- and perhaps, as you said, there are areas that the laboratories have done well and taken care of, and if we can leverage those, then those will be leveraged. You know, one would leverage those into whatever framework one comes up with, but clearly -- and it is not just us. There has been a lot of discussion as to what are

the gaps, and how are those gaps going to be filled.

DR. LINDER: Yes, and I acknowledge that potential gap, but I also see it as the ultimate responsibility of the medical director to fulfill that gap. That is part of the medical director's responsibility, to make sure that the services they are providing, just like any medical professional, are relevant to the clinical application.

So I agree that maybe there is not adequate structure around that, but I also don't think that -- I also still think that that is a responsibility of the medical director, and that is where it really should be driven.

DR. GUTIERREZ: And who holds them responsibility?

DR. LINDER: Well, as any medical professional is held individually responsible. Just like a surgeon is held responsible for their clinical practices, laboratory directors are medical professionals. They should be held responsible in a similar fashion.

DR. GUTIERREZ: But I think the issue here is exactly that there is a lot of people who don't believe that those are being held responsible.

DR. LINDER: Well, that may be the case, but

what I am saying is the approach to this could possibly be driven through more traditional mechanisms of how the laboratories are -- how the quality of the laboratories are overseen and maintained, rather than from the testing perspective. That is what I am getting at.

DR. GUTIERREZ: I would encourage you then to submit something to the docket, giving us an idea of how that framework would work, and putting together something that we could move from.

DR. LINDER: Right. Well, my question was really driven by how far along in that process had the FDA gone in trying to determine which path they thought was --

MR. GUTIERREZ: As we have said, we really have not. If you can come up with something that is credible and that makes sense, we would definitely take it into account.

DR. LINDER: Thank you.

MR. WEINZIERL: Charlie Weinzierl from Children's Hospital, Boston. A quick question about the availability of some of the genetic tests, in particular.

I am wondering if any of the panelists would like to comment on the latest regulations around patentability of certain genes and the impact that has on the availability of these

tests and being able to get a second opinion and things like that.

DR. GUTIERREZ: Probably not. This is really not the forum, and there are other forums that are looking at this, like SACGHS. So I think that would be a better place for comments and suggestions.

MR. WEINZIERL: I tried.

DR. GUTIERREZ: Okay. So if there are no other questions, we will go ahead and start on the next round.

So we are going to essentially go through several public presentations. These are to take more or less five minutes, and Katie Serrano will be sitting in the corner here. She will let you know when you are approaching your five minutes. Please try to stay within the time frame so that everybody gets a chance to speak.

MS. SERRANO: Yes. Because we are starting this morning, there is a little bit of flexibility in our time. Anybody who knows me knows that I really like things to run on time. So I will be giving time signals. I will give one minute, 30 seconds, and a stop. You don't have to stop immediately, but please don't go beyond about 30 seconds.

For those that have given me slides, I will cue those up prior to you speaking.

DR. GUTIERREZ: And before we start speaking about slides, we have been asked if those can be made available, and we can make them available. You won't be able to actually see them in the webcast, and the webcast is going to be available for a year. But if you prefer the slide stack itself, we can make this available. We won't make them available in our website, because we need to comply with the 508 laws, and most slides don't.

What we can do is you can e-mail Katie and ask her for these slides, and she will provide them to you.

MS. SERRANO: I guess our first speaker this morning would be Roger Klein. He can begin to make his way up here.

DR. KLEIN: Good morning. I am Roger Klein. I am Medical Director of Molecular Oncology at the Blood Center of Wisconsin, and Clinical Assistant Professor, Pathology, at the Medical College of Wisconsin.

Today I am speaking on behalf of the Esther and Hyman Rapport Philanthropic Trust, a Cleveland based private foundation with broad interests in health care.

By way of background, I am a physician with over six years of post-graduate medical training. Much of that training

has involved the design, development, validation, oversight and interpretation of laboratory developed tests, including molecular genetic tests.

I am certified by the American Board of Pathology in clinical pathology and molecular genetic pathology.

Pathology is a diagnostic specialty, and laboratory developed tests, as we have heard, has historically been intrinsic to pathology practice. LDTs are pervasive in the clinical laboratory and have been at the center of striking advances in medical care.

Magic Johnson, despite infection with the HIV virus, can look forward to a long life. His former teammate, Kareem Abdul-Jabbar, who last year was diagnosed with chronic myelogenous leukemia, has a far greater prognosis than he would have 25 years ago when the five-year survival was 30 percent.

Acute Promyelocytic Leukemia is the first cancer for which a cure based on a molecularly targeted therapy can be achieved. In 1980 it was a death sentence. Now 80 to 90 percent of patients are cured. None of these advances could have happened without laboratory developed tests.

My mother and my aunt were afflicted with a severe inherited neurological illness called idiopathic torsion

dystonia. When our friends, Susan Bressman and Stan Fahn at Columbia Medical School, set out to understand the genetics of this disease and to find the causative gene, I and my family members donated samples to help make this a reality.

They soon discovered that gene, and shortly thereafter Massachusetts General Hospital set up a diagnostic test for the disease. It was a laboratory developed test that allowed me to have my wonderful, beautiful daughter, Ariel.

If FDA had been regulating laboratory developed tests, would these public health benefits have occurred? What of our academic medical centers, the sites of so much of our medical innovation? Few, if any, have the resources to submit their excellent services for FDA review.

What would be the effects on patient care, teaching, and clinical research? Is there sufficient evidence for systemic harms from laboratory developed tests to justify the imposition of costly new regulatory burdens?

FDA has acknowledged the importance of the relationships between pathologists, our treating physician colleagues, and our patients. Communication between pathologists and treating physicians is essential to allow patients to optimally benefit from improvements in diagnostic testing, but

would FDA regulation drive testing away from the patient's health care setting and the supervision of the patient's pathologist and treating physician?

A number of for profit companies that sell test kids nationwide have complained that they are treated unfairly relative to pathologists and other laboratory service providers. However, the nature and economics of the activities of these groups are very, very different. It would be neither sensible nor fair to treat them identically.

Therefore, it is our belief that the only level playing field with which FDA should be concerned is that of the patient.

Thank you very much. Appreciate it.

MS. SERRANO: The next speaker is Cara Tenenbaum.

MS. TENENBAUM: Good morning. I am Cara Tenenbaum. I am with the Ovarian Cancer National Alliance, a patient advocacy group that represents the more than 170,000 ovarian cancer survivors, their families, and those who are at high risk of developing ovarian cancer.

Probably many of you know that around 22,000 women will be diagnosed with ovarian cancer this year. Fifteen

thousand women will die of the disease.

The difficult thing with ovarian cancer is that it is often diagnosed late. There is no reliable early detection test, and I know that probably many of you in the room and many of you watching this are working on that, and we really appreciate those efforts. However, we have had some issues around ovarian cancer specifically.

I don't know if all of you know about them. So I do want to share them with you.

A couple of years ago -- Actually a number of tests have been brought to market without sufficient clinical data to verify that they are good diagnostic tests for ovarian cancer. As I am sure you all have read in the newspaper, if people are misdiagnosed with ovarian cancer or told they are having a recurrence when they are not, they can really suffer some serious harms, not the least of which is unnecessary chemotherapy, unnecessary surgery, surgical menopause.

Of course, those are not done without doctor influence. However, when there are tests that are brought to market that aren't necessarily reliable, it creates a greater burden for doctors.

I am sure I can't imagine what it is like talking a

patient out of getting a test, but for my organization, we have had to explain to patients what tests mean, what they don't mean, where the published data is or isn't, in some cases, and it is really difficult.

I still get nasty letters asking why we haven't endorsed certain tests for which we haven't seen Phase 3 data or what the result of a genetic test means.

The Center for Genetics and Public Policy published a really nice chart of what all the genetic tests on the market test for, and some of them are really interesting: Whether or not you have the dancing gene or the shyness gene, which my father says took so long to find, because it was hiding behind another gene. But you know, ovarian cancer is kind of in this constellation with breast cancer, colorectal cancer, uterine cancer.

So just counting it up, there are 30 tests, three tests for the Ashkenazi Jewish mutation, 13 tests for breast cancer, nine for colorectal cancer, one more for colon, two for endometrial cancer, and five for ovarian cancer.

So I called up some of these places and kind of tried to figure out what they mean. Why are there 13 tests for breast cancer, but five for ovarian? What does that mean, and is

that kind of valid?

I am having a really hard time as someone who -- I consider myself fairly well educated, but I am not a doctor. What does it mean to have a low penetrance gene? Does that mean I should go talk to my doctor about having an oophorectomy?

What does it mean when you get these results, and when you get them at home alone without a genetic counselor or a doctor? How are you supposed to interpret that? When you get a test that tells you might have Alzheimer's, what are you supposed to do about that?

So my concern here, and the reason I am so glad to be able to present -- and thank you very much to the FDA for holding this meeting -- is that patients need to have accurate information. Of course, our concern is access and price, but access to a test that is not reliable or an inexpensive test that doesn't give you good information isn't really that useful.

So I do urge that in this meeting and as we move forward we look at the accuracy of the tests and the value of them to patients.

Thank you very much.

MS. SERRANO: Our next speaker is Richard Hockett for Affymetrix.

DR. HOCKETT: Good morning. I wanted to make just a few general comments in my five minutes of fame. I guess I don't get fifteen.

I am the Chief Medical Officer of Affymetrix, a manufacturer of devices that are used in, and I wanted to do about three things with these five minutes. First, I didn't realize we were keeping score, but in the spirit of the recent World Cup, I was actually asked about a half a dozen times out in the hall was I pro or against regulation of laboratory derived tests.

I actually will come down on the side of regulation, because left to our own devices -- and in this case, pun is intended -- manufacturers will push the envelope and, as we have seen a list already of times when that envelope is pushed, you can compromise patient safety.

The key here, though, is to make sure that that regulation doesn't stifle innovation and stifle access of patients to devices and answers that they couldn't get any other way that will impact that health.

So while I do believe that we need both FDA and CLIA type oversight to ensure that laboratory tests are safe, effective and accurate, we have to use our creativity, and that is point number two. All groups aside from this, I have a plea for

creativity to make sure that we don't shut off what has, and you have seen, become a very important part of application of medicine to patients.

The final thing I would like to do is to talk to the FDA a little bit. While traditionally laboratory derived tests and the formation of in vitro diagnostics have been separate pathways. I think many manufacturers now are looking at laboratory derived tests as a step-stone to in vitro diagnostic tests, that they are indeed not completely separate pathways to development.

The reason for this is because, with the advent of these new technologies, very complex tests, and the expense of going all the way to in vitro diagnostics, when you first start off, you don't know if somebody is going to use the test or if it does have medical utility sufficient to become a diagnostic.

So the pathway to get some of those answers has been -- has become laboratory derived testing route. Now we may not like that that has been inserted in the middle of the path toward in vitro diagnostics, and indeed there are some aspects of that that may be troubling.

We then have to come together collectively and figure out how to get a better stepping stone for the application of these new technologies to in vitro diagnostics, and that is again

where I would plea to our creativity to make sure that those avenues are there so that we don't shut off the application of what has become these very important modalities. Thank you.

MS. SERRANO: Our next speaker is Sharon Terry.

MS. TERRY: Thanks very much for this opportunity. I am from Genetic Alliance, which is a coalition network of about 10,000 organizations, about 1200 of which are disease advocacy groups. We are transforming health through genetics, so are very concerned about these issues. I am also the mom of two kids with a genetic disease, and this is how I got into this business, so to speak.

We really want to look at what matters from the point of view of the patient and the consumer of genetic tests, and access to safe and effective treatments is most critical, of course. Accelerating the solution for thousands of these disease would be our goal with good diagnostics, and the policies and systems that would support all the above are critical.

What about LDTs? I think that diagnostics are absolutely revolutionary, if used effectively, and that medicine will essentially be transformed through diagnostics.

In vitro diagnostics, I believe, are different than

devices, and the current system is ill suited to enable efficient approval or clearance of advanced diagnostic tests with meaningful claims that reflect how the tests will be used in patient management.

The classification framework that we would recommend would be relative risk of information provided by the diagnostics, and that we consider the severity of the disease and the context of the use of the test.

The standard should be flexible and dynamic, which is a difficult thing, certainly, to do, but absolutely necessary in this current age, supported by evidence that has been deemed competent and reliable to make the intended claims, and that also the lack of evidence that is consistent with what experts in the relevant field consider to be sufficient for decision making at the time that the test is being developed.

The system has to be flexible. It can't be black and white when we are considering safety, and that is supposed to say efficacy. Spellcheck took care of that word. Determining methods to communicate what is known and also what is not known, to pay attention to rare diseases during this development will be critical. That is sometimes left out, and that patient care not be disrupted during this time, including the acceptance of

currently marketed tests by payers.

So the bottom line, I think, is a mandatory diagnostic test registry, a risk based classification, a consideration of context throughout, and that a sensitivity to rare disease and personalized medicine would be important. Thank you.

MS. SERRANO: Our next speaker is Benjamin Salisbury.

DR. SALISBURY: Good morning. My name is Ben Salisbury. I am the Vice President of Clinical Genetics at PGxHealth.

PGxHealth, which is a division of Clinical Data, develops and commercializes therapeutics and genetic tests to help providers diagnose serious diseases and predict drug safety and efficacy.

We are perhaps best known in the genetics community for our Familion brand of sequencing-based genetic tests for mutations that predispose to rare heart diseases, most notably long QT syndrome and hypertrophic cardiomyopathy.

The long QT test has been available for about six years, and has served thousands of physicians, patients and their families.

PGxHealth's LDTs are provided through its

CLIA-licensed lab, and ar available only through physicians and other licensed health care providers. All test results are then returned only to these clinicians.

Several PGxHealth biomarkers have been out-licensed to other labs and IVD manufacturers to ensure wide physician access in either a CLIA or FDA approved format, depending on the needs of the situation.

I want to make the point that market forces are very effective at determining the use of LDTs. Clinicians and payers are traditionally slow adopters until there emerges a clinical consensus in the medical community on the utility of a test. Therefore, currently under-utilization, not over-utilization, is the norm.

In many cases, even FDA approval and inclusion of, say, pharmacogenetic information in a drug's label does not appear to have a significant impact on utilization. For instance, the UGT1A1 test for Camptosar, TPMT testing for the thiopurine drugs, both of which are related to adverse events and safety, or more recently the efficacy or dosing related tests for warfarin and clopidogrel.

LDTs have proven to be a valuable, routine, and necessary part of clinical practice for many years, and examples of

tests that either have been or still are LDTs, HIV viral load testing, the HER-2/neu test, and long QT syndrome.

Over-regulation would clearly hamper innovation. Over-regulation of LDTs would discourage research, development, and commercialization, the translation of science, of these new clinically important tests. This is because small initial markets, lack of reimbursement and costs associated with physician and payer education already pose significant barriers. Additional regulation will further deter test development.

Small laboratories, it is widely known, assume most of the scientific and commercial risks associated with developing new tests, and will be most severely impacted.

Under CLIA, our company was able to justify investment in developing the long QT syndrome test. If we had had to go through extensive FDA approval or clearance, we likely would never have undertaken that, and testing for long QT syndrome might still be done only in the context of research labs 14 years after the discovery of the first gene.

In summary, the ability to develop and market LDTs is key to bringing new clinically important tests to the health care system. We want to react as quickly as the science allows.

Adoption of new tests is naturally limited by the

market. Over-regulation would hamper innovation. Therefore, PGxHealth opposes burdensome regulation of physician ordered LDTs.

Finally, a closer examination of the risks of the current system versus the risk of new regulation is warranted. Perhaps the FDA should commission a study by the Institute of Medicine to examine the costs and benefits of the current system versus any intended or considered options for the future.

Thank you very much.

MS. SERRANO: Our next speaker is Eric Lawson.

MR. LAWSON: Good morning. My name is Eric Lawson of Voisin Consulting Life Sciences. I am also the Chairman of the Companion Diagnostics Working Group of the Association of Medical Diagnostics Manufacturers, and this presentation is representing a consensus of that working group and not necessarily the totality of the AMDM membership, which includes IVD manufacturers large and small, CROs and providers of LDTs, also of using IVD, meaning IVD labeled commercially distributed in vitro diagnostics.

The Working Group acknowledges the use of laboratory developed tests for rapidly developed limited use testing to provide the capability to unmet patient needs.

However, we do not support the use of laboratory developed tests for companion diagnostics.

What is a companion diagnostic, and how does it support the structure of personalized medicine? A companion diagnostic is a test which is critical in terms of its information to ensure the safety and efficacy of modern targeted molecular therapeutics. The companion diagnostic is identified in the drug label.

The companion diagnostic is intended to ensure that the right patient receives the right drug at the right dose at the right time. Companion diagnostics require a close collaboration between the diagnostic development and the drug development. There are labeling and collaboration required as well in terms of coordination of the labels, and also a misuse of the analytical results of the diagnostic could lead to a misuse of the drug, and thereby cause patient harm.

The targeted modern molecular therapeutic drug or biologic requires clinical data submitted to the FDA for review. An LDT does not require independent review of this data. An IVD does.

The targeted therapeutic drug must be approved by FDA before release and widespread use. An LDT does not.

IVDs do require clearance or approval by the FDA.

The targeted therapy must meet strict regulations under FDA oversight for labeling, for the claims, for vigilance, and to report adverse events to the FDA. LDTs are currently not subjected to such FDA oversights, whereas in vitro diagnostic labeled tests require FDA oversight for their labeling, for claims. There is the MDR process for reporting of adverse events.

Also, the targeted therapeutic drug must meet FDA's current good manufacturing practices. LDTs do not have to meet the GMP or the QSR regulations, whereas an IVD labeled product must be manufactured under the 21 CFR Part 820, quality system regulation.

FDA has made statements in some of their Advisory Committees relating to how drugs and companion diagnostics should be linked and/or reviewed by the FDA.

Some limitations of laboratory developed tests in the CDx context are that there is no transparency to the public regarding the LDT claim. There is no opportunity for FDA review, and it is not evaluated by the FDA. There is a lack of labeling coordination with the drug company, and there is no possible coordination between the multiple centers within FDA to review an LDT, and there is no mechanism currently for adverse event

reporting of any LDT response.

We are recommending that there should be four sides to the table for any review of a companion diagnostic. This includes both the pharma and the diagnostic developing partner, as well as both the CDER or CBER therapeutic evaluation by FDA, and the CDRH's OIVD.

We are also proposing a three-tiered risk based approach to ensure that the language and the consistency of drug labels and companion diagnostic labels will identify when a companion diagnostic is required or recommended or for information only, and that such companion diagnostics be FDA regulated products.

In conclusion, while we support laboratory developed tests for rapidly developed limited use areas where the patient need has been unmet, we also encourage regulation or adequate control of LDTs, and we feel that, when a diagnostic assay will be used to make an important therapeutic decision in a test such as a companion diagnostic, that the LDT platform is not appropriate, and we, therefore, propose that companion diagnostic tests must be cleared and approved by FDA.

So if you have any questions, you can contact me at Voisin Life Sciences or any member of our Companion

Diagnostics Working Group. Thank you very much.

MS. SERRANO: Our next speaker is Dan O'Leary.

MR. O'LEARY: Thank you for the opportunity to speak today. Ombu Enterprises is a small New England based consultancy. We focus on operational excellence. Some of our clients include medical device manufacturers, and some of them include in vitro diagnostic manufacturers.

As we have heard, there are two paths, this bifurcated approach, to regulation. So FDA could potentially be regulating or not regulating, as the case may be, the same device through these two different paths.

Manufacturers follow the traditional approach of clearance, approval, registration and so on. Laboratories follow an approach that I am going to say is essentially based on CLIA. We have heard that that is not exactly correct, but that is how the laboratory piece of it is managed.

So we are going to urge that FDA apply the same regulatory approach to both forms of the device. So in standard business practice, we often talk about making a make versus buy decision. That is, in this context, the choice between a test kit or a laboratory developed test.

In the public health and regulated industries, this

decision is a lot more complex. They are not necessarily the same kinds of decisions that we would find that the regulatory bodies are going to bring particular expertise to the make versus buy decision, but the difficulty here is that the different systems don't provide equal level of assurance all along the supply chain, the end of the supply chain being the customer.

So the point of view is to look back into the supply chain from the customer's point of view. The customer in this case is the patient.

If you look in the ASR regulations, you will find, for example, that laboratory developed tests require a disclaimer that the test has essentially not been cleared or approved by the FDA. So we already have this camel's nose in the tent that tells us that there is a difference in the market.

So we believe that FDA has four options. One is to do nothing, and that is, continue along the current scheme. The second is to the greatest common multiple approach. That is, apply the current manufacturer's requirements to all LDTs, including -- to all IVDs, including laboratory developed tests. That is, all the laboratory developed tests should follow the same regulatory scheme.

The least common denominator approach goes

the other way. If the current regulatory scheme is satisfactory for those kinds of tests, why isn't it satisfactory for commercially marketed IVD test kits? So one approach FDA could take is to lower the regulatory burden so that IVD manufacturers have no more stringent requirements on developed test manufacturers, or consider some common ground, the union of those two things.

Now we don't anticipate that FDA is going to reduce the regulatory burden on IVD manufacturers. So our recommendation is that LDTs and IVDs be treated the same way, that they have the same regulatory structure that LDTs, require registration and listing, approval of clearance based upon risk classification, and I don't consider this to be an onerous burden.

We have already seen that 50 percent of the IVDs are in Class I. So it may turn out that most of this won't apply to LDTs. LDTs are manufactured by manufacturers, although we call them labs as well. So I believe that QSR should apply as well as postmarket surveillance.

I am going to give you two models that I think have been quite successful in helping make the transition. The first is QSR. If you remember when QSR first came out, there was a series of satellite broadcasts -- Kimberly Troutman, for example, did a lot of explanation about what is going on -- and a subsequent

deferment of the design control portion for one year until everybody could get up to speed.

Similarly, there was a change in regulations for single use devices by hospitals. Hospitals are now manufacturers, and there was a transition period. FDA was quite successful in implementing that.

I believe, therefore, the strategy exists to bring a level playing field to all of the manufacturers of IVDs, whether they be commercial houses or laboratories. Thank you. MS. SERRANO: Our next speaker is Elizabeth Kearney.

MS. KEARNEY: Good morning. I am a Certified Genetic Counselor and President of the national Society of Genetic Counselors or the NSGC, the professional association for genetic counselors.

For those of you with no background on genetic counselors, we have specialized graduate degrees in medical genetics and in counseling and work in a broad range of specialties and settings, which include patient care in hospitals and clinics, as well as in diagnostic laboratories.

The NSGC supports the FDA's efforts to examine the current regulation of laboratory developed tests, and wishes to raise two areas of particular concern for consideration as

regulations are drafted.

These are, number one, patient access to genetic testing for rare genetic disorders, and number two, the risk of misinterpretation of genetic testing, despite regulatory approval.

As was stated by the speakers this morning, historically most genetic tests were utilized by genetics professionals, namely, genetic counselors and medical geneticists, to serve patients affected by rare single gene disorders.

The needs and expectations of these patients and their providers have not fundamentally changed over time. They want and need analytically reliable genetic testing that allows diagnosis, directs medical management and treatment, provides psychological benefits, and assists with obtaining social services.

With increased regulations -- Although increased regulations may be very important because of the expansion of genetic testing into areas outside of rare genetic disease and into non-disease causing genetic factors, overly burdensome requirements aimed at demonstrating clinical validity in broad populations may impede patient access to tests for rare and orphan genetic diseases.

The advances in cardiac genetics are probably a good example. Ten years ago, if someone had a family history of

sudden cardiac death, there would have been pretty limited information available to them. Today, we have multiple genetic tests available, and one does wonder, if there were really stringent regulatory requirements, perhaps those tests would not be available or would just be emerging from research and development today.

Therefore, I am glad to hear that there is sensitivity to the needs of these smaller populations and, certainly, recommend that regulators continue to accommodate the needs of those populations.

Genetic counselors interact directly with patients and providers in the delivery of genetic information, so are well qualified to comment on the expectations that patients and clinicians have of genetic testing.

Patients who are seeking genetic services are not always looking for a particular genetic test, but rather have questions about conditions that run in their families. They rely on their health care providers to understand how to apply genetic testing, and typically assume that any genetic testing that is ordered is valid and useful for their particular situation.

In general and across specialties, clinicians trust the analytical results of LDTs, and state and Federal regulations

should ensure that this trust is well placed.

Therefore, the NSGC recognizes the need for improved oversight of genetic testing in light of the expansion of testing. However, genetics trained professionals recognize that clinical validity is determined not only through available evidence but also in light of individual patients' medical and family history.

If genetic test deemed clinically valid for large populations receive FDA clearance, other clinicians with less of a basis in genetics may assume that these tests are, therefore, safe to apply very broadly to their patient base.

For example, a primary care doctor may reassure a patient who gets a genetic test result demonstrating a lower than average for diabetes, even if she has a gestational or a history of gestational diabetes or a family history of diabetes. A genetics professional would recognize this as a sign that there are probably other genetic factors at play other than those tested.

Bringing such tests into mainstream acceptance with FDA approval could result in outcomes that would actually conflict with the intention to protect public health.

The involvement of a genetic counselor, whether directly in patient care or indirectly in consultation with a physician or through the diagnostic lab, can help to mitigate these

risks but, obviously, that involvement is not required. Future regulation may want to address such involvement for genetic testing through CMS or other Federal programs.

The NSGC appreciates the opportunity to comment today and we will provide further guidance as proposals are presented, and we do believe that there are proposals, even some that have already been floated, that would allow for a balance of access and protection of patients.

As health care providers specially trained in delivering genetic information, genetic counselors have a very strong interest in ensuring patient access to genetic information, while protecting them from harm.

Thank you.

MS. SERRANO: Our next speaker is Daniel Poscover.

MR. POSCOVER: Hello. My name is Dan Poscover, and I am the CEO of PharmacoGenetics Clinical Advisory Board. I made it in plenty of time, a whole 20 minutes to spare. I took a flight down this morning. I will try to be brief, kind of focus on outcomes data matters utilizing third party review of LDTs.

Regulation for LDTs has to be a stepwise approach. It can't be all of a sudden, and I will end with who we are, just because I

figured I will run out of time anyway.

So PharmacoGenetics is a decision support and resource, trying to enable personalized medicine. Physicians require increasing level of evidence. Analytical accuracy and clinical validity, which is what the FDA IVD process does, versus peer reviewed outcome and data, which is what clinicians want and how they make decisions. Clinical community's acceptance is based on peer reviewed articles rather than regulatory approval, utilizing third party LDTs.

So it is really about balancing public health and innovation, and one solution that we can think about is the Critical Path Initiative has spent a lot of time thinking about ways to make this better, and they have a solution that a positioned and they can facilitate it.

Patients and clinicians trust peer a reviewed system such as structure, such as a structure that could provide checks and balances required for a fair and uniform process. They are also concerned with liability issues. So they would do anything they can.

So such an independent organization is an independent diagnostic standards organization, an industry driven solution in collaboration with the FDA. The key to this is a

stepwise process. You create steps and do one at a time, and don't jump into it.

Require products to be developed under design control. Leverage reviewed process, and standardize the system. Require a transparency of all validated data, and this would be a huge leap, which is create a repository of cohort banks across therapeutic areas combined with anonymized longitudinal health records. I realize that is a leap of maybe 20 years from now, but that would help the system.

Then who is PCAB? We provide knowledge, easy searchable data, third party validation, and guideline standardization. We have 15 clinical advisory board going through a database of more than 500 peer reviewed articles per month, which is searchable and easy to understand.

Any questions or want the presentation? Feel free to e-mail me. Thank you.

MS. SERRANO: Our next speaker is Michael Stocum.

MR. STOCUM: Good morning. I would like to take a moment and thank the FDA for convening this meeting to discuss this important issue, and also providing me an opportunity to comment on it.

I represent Personalized Medicine partners, a firm that I founded six years ago whose mission is to integrate diagnostic and therapeutic development throughout clinical and commercialization.

In my remarks, I will attempt to address a couple of points relative to the questions that FDA raised initially when convening this meeting, and that was how this might impact patients and clinicians with a focus on clinical development, and also what might be the benefits, and I will also explore some case examples briefly as we go through the slides.

My views, in fact, are influenced by a variety of cases experienced over the last 15 years that include things like working on HIV-1 RNA from the earliest assays through to its ultimate use as a surrogate endpoint for registration of many of the novel, at the time, protease inhibitor drugs that are now the backbone of combination antiretroviral therapy that has been extremely effective in reducing suffering from HIV.

I was also involved in the development of a novel open source nucleic acid testing kit that included standards and a platform upon which end users would appropriately validated primers and probes could conduct their own home brew assays or laboratory developed tests, as they are now known.

I was also involved in an Abacabir Hypersensitivity reaction to Abacavir test that was developed at GlaxoSmithKline back in the late Nineties and early 2000s when this team discovered that indeed there were HLA-B5701 marker that was relevant to patients having response to Abacabir that was a serious adverse event, and the commercialization path for that initially was as a laboratory developed test.

Then lastly, some of the views I think people have mentioned before that we are learning from are the Hercep Test, Herceptin story, and the various tests that have developed since that point for Her2. There are examples surrounding k-ras that are very timely now, and we need to recognize that whatever regulation is developed should take into account multiple platforms across a variety of therapeutic areas.

One thing to point out is that this is a very unique issue that, for the most part, the U.S. market is wrestling with. Those of you that might develop products globally recognize that many other geographies do not enjoy the same laboratory network framework that we have here in the U.S., but there are some reasons that this has evolved in the U.S., and I have listed a couple of them that are business related.

Perhaps most importantly is the second part, and

that is the failure of the timing of in vitro diagnostic development to sufficiently align with therapeutic development in order to enable a seamless co-development of companion diagnostic and therapeutic products.

There are some current examples, again, that are on the market that bear this out. One, in fact, is Miravoric and Trofile, and also if you look back in history a bit further, you can see the HIV sequencing that was coming into the clinic and providing useful information for clinicians yet again had to be kept mostly as a laboratory developed test, because the technology was evolving rapidly, as were the markers.

So what are the key needs that we should focus on for this discussion? In my opinion -- this has been stated a number of times, but I will state it again -- there is an important need to maintain this innovative approach to developing new laboratory medicine tests, and that will enable patient benefit, and we need to maintain that access to the CLIA-LDT route.

That is critical to care. That has been stated earlier as well. However, it is important that we begin to standardize more carefully around the testing reagents and, certainly, have some sort of oversight or arbitration about claims that are made on LDTs so that they may enhance the physician's

ability to better apply the tests that are developed in combination with therapeutics or even independent of therapeutics.

Lastly, although not the purview of FDA, there is an important market force, and that is value based reimbursement would help drive investment into areas that would help to generate the business case, so that one didn't have to go only down the LDT route.

So my mentors always told me, offer solutions if you are going to talk about problems. So I am offering up a few solutions to consider here, some of which, again, are being raised by other speakers and by the FDA itself.

Test registry: As we mentioned earlier, the NIH has begun a genomic test registry. That is underway. There are a variety of other test registries available, and perhaps a central clearinghouse for that could be very useful.

Accepted sample repository: A previous speaker noted the importance of these. I hope that we can do it in less than 20 years. There are certainly other countries and other geographies that are doing it now today.

Broader availability of test standardization programs: There are some wonderful examples that already exist through a variety of organizations, and we could certainly

expand that effort.

I also would point out that we might consider a progressive authorization approach. This has been successfully used in certain therapeutic development areas, and it certainly could enable better development of tests, yet again with the standards and regulation.

Appropriate reimbursement prior to a kit being cleared or approved would also allow for better market adoption and change the dynamics of what holds back current tested option today.

Lastly, postmarketing surveillance programs would be very important in any of these examples.

There are a variety of stakeholders that I will not go into at this point, but we need to make sure we have engaged and heard their opinions and, of course, the sun is setting on the past, and we need to look forward, and I look forward to hearing new regulation and appropriate coverage of this market.

If there are any questions or requests for a presentation, please feel free to e-mail me.

MS. SERRANO: Our next speaker is Dierdre Astin.

MS. ASTIN: Well, my presentation says "good

afternoon," but I guess I will have to change that to "good morning." I will also move my thank you for the opportunity to speak up to the front, in case I run out of time.

So my name is Dierdre Astin. I am speaking on behalf of the New York State Department of Health. I am the Director of the Wadsworth Center's Clinical Laboratory Evaluation Program. It is one of the regulatory programs in the Division of Laboratory Quality Certification for the Center.

I oversee the intake and review of non-FDA-cleared and laboratory developed tests by program personnel and the scientific staff at the Wadsworth Center. We are known collectively as the Center's Clinical Laboratory Reference System.

I will be speaking from the perspective of over 10 years of experience involved in the oversight of these assays, and I believe that this process has a positive impact on patient care.

First, I will describe our program. Clinical laboratories have to hold a valid New York State permit, if they are either located in New York or accepting samples from New York.

Permits are issued based on successful participation in our CLIA approved proficiency testing program, an on-site inspection, and a review of laboratory personnel

requirements, which include certification of a doctoral level laboratory director.

Over 980 laboratories currently hold permits with our program, and our program -- Labs holding permits in New York are exempt from CLIA certification, which means that CMS has reviewed our program, and based on a review and evaluation that our program is at least as stringent as CLIA, labs holding New York state permits don't have to be registered with CLIA in New York State.

We support the oversight and review of LDTs as a means of ensuring that assays used for patient care meet the highest standards of clinical and analytic validity.

So what we have done is over 4,000 assays have been approved for New York State use since we started keeping track with a database in 1997. Methods reviewed range from those using more common methodologies to those using complex genomic tests, combining sequencing data and personal health information.

A relatively small number of assays are actually denied, but the majority of the assays reviewed are returned to submitting laboratory for correction of errors, and must be resubmitted.

The were 534 new methods and 458 resubmissions received in 2009, and the highest area of activity, as you can imagine, are in the areas of oncology and genetics.

Packages varied from modifications to FDA approved tests, which we consider a laboratory developed assay in New York State. For a modification, labs only have to submit usually as a first glance, just a patient report and a procedure, showing what they have modified and the validation for the modification.

Then a full validation package is required for a true laboratory developed test. This could range from a package including the full SOP and original instrument runs, statistical modeling if algorithms or statistical software is used.

In 2009 these reviews resulted in 442 requests for additional information or clarification of errors. Errors included and identified in material submitted ranged from inaccuracies in procedures to inadequate design of validation studies which failed to address critical performance characteristics, including performance of the assay with different specimen types, effects of inhibition and/or assay interferences, establishment of correct reference ranges, limits of detection.

Failure to adequately address these

considerations can significantly affect assay performance and results interpretation, and cause misleading and even erroneous test findings with potential to impact patient care.

In some cases, the clinical and/or analytic validity of an assay cannot be demonstrated, and the assay is denied. We believe protecting patients from treatments that may be based on inaccurate test data -- examples of assays that were denied include an analytically flawed flow cytometric based chemotherapeutic sensitivity assay, stand-alone CSF based serologic tests that lack analytic and clinical sensitivity, non-FDA-cleared commercialized test for Candida antibodies, tests that is of questionable clinical validity, including botanical sensitivity tests, tests for nonspecific proteins in urine which claim to diagnose patients with Alzheimer's disease, and IgG assays for food sensitivities.

New York State assay reviews for genetic testing include an assessment of the clinical validity of the mutation and an analysis of the statistical algorithms used to determine risk or predisposition, and in some cases, the claims of a laboratory to accurately identify disease and/or assess risk have been challenged.

The Center has also challenged the analytic

validity of assays with customized proficiency tests. A laboratory offering an antigen detection assay and a matrix where cross-reactive material was highly probable submitted the assay for review, and skepticism regarding the data in the validation packet prompted Center scientists to design a panel of proficiency test samples to assess the reliability of the assay.

The challenge including replicates to which the laboratory was blinded, and they reported their results as positive, indeterminate, and negative, even though they were all the same material.

This proved the assay lacked analytic validity, since the laboratory could not obtain the same result on identical specimens tested at the same time and in the same laboratory.

I would just like to close by saying, in this era of ever increasing complexity in laboratory medicine, clinicians cannot reasonably be expected to be well versed in the nuance of laboratory test selection and interpretation.

Patients have access to more health information than ever before, but there is still the concern or the common misconception that test values are absolute. Patients, and even some clinicians, regard laboratory tests as definitive, and sometimes fail to recognize that they need to be interpreted along

with other symptoms and clinical history, and not relied upon completely.

Concerns about health care costs demand that only proven and effective laboratory tests are used, and that good science and not marketing tactics drive these choices.

It is for these reasons that the review and approval of non-FDA-cleared and LDTs is best conducted in an objective manner and in a regulatory environment.

I will say thank you again.

MS. SERRANO: Our next speaker is Mary Pendergast.

MS. PENDERGAST: Thank you. Having spent much of my adult life with the Food and Drug Administration, I have great loyalty to the agency, but today I want to speak pointedly about the FDA's attitudes toward the regulation of the testing industry.

I represent testing companies, but these comments are my own. It would be incredibly unfair to attribute them to any company.

As a bedrock principle, all tests that are similar in risk should be subject to the same level of FDA oversight, regardless of who sells or conducts the test. On this issue, my

views are in line with those set out in the Genentech Citizens petition. I also agree with Genentech that FDA should look first at the tests used to make life and death therapeutic decisions.

In my opinion, it is unlikely that physicians and consumers pay attention to who provides a test or what silo of FDA regulation the test falls into. However, FDA should not regulate based on my opinion or on the opinions or anecdotes of others or indeed on the opinions and anecdotes the agency is already relying on to make policy.

Rather, FDA should conduct research into physician and consumer understanding, rather than making decisions based on what the agency thinks it knows, which may be wrong or based on paternalistic assumptions.

One speaker stated that FDA would regulate particular tests if they were, quote, "beyond what makes us uncomfortable." FDA officials have also been quoted as saying that the agency intends to regulate direct-to-consumer genetic tests as high risk, because consumers will not understand the information they are receiving, and they may do something that someone at FDA thinks is irrational.

These fears are out of date and paternalistic. While FDA has been wringing its hands over what consumers may

or may not do, scientists are studying the issue, and the studies on consumer behavior must be considered before any action is taken.

Literature now shows that, when a person seeks to learn genetic information and finds out what he or she wants to know, the person understands the information, appreciates the information, and does not make rash or unconsidered action.

I encourage FDA to read the studies from the National Institutes of Health, academic researchers and others. They have studied empirically what happens when consumers seek genetic information and receive the information they seek. The answers are not what FDA thinks they are.

It is also not only old fashioned and downright paternalistic for FDA to determine what a person may or may not know about that person's own body. It also may violate the First Amendment.

Truthful and non-misleading information is good. Knowledge is good. Even preliminary information is good, as long as it is properly described. And this isn't just me saying this or me talking.

The FDA said the exact same thing 34 years ago when Virginia tried to regulate the information pharmacists could give to consumers. The Supreme Court said, "There is, of course,

an alternative to this highly paternalistic approach. That alternative is to assume that this information is not, in and of itself, harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them."

The question is: Will FDA leave the channels of communication open? The First Amendment requires that the FDA impose no greater burden on speech than is required to stop false and misleading speech, which brings me to my last point.

In the New England Journal of Medicine, the Commissioner stated that FDA was going to impose pre-review on some tests and that the FDA planned to have an efficient review process.

This meeting is an important first step, but based on actions to date, there is not evidence that FDA understands how to achieve the Commissioner's goal.

CDRH does not now even credit the decisions made by the Center for Drug Evaluation and Research. Yet in the future CDRH will have to rely on not just the rest of FDA but on the national Institutes of Health and others to evaluate the growing field of bioinformatics.

CDRH also needs to fully appreciate how few applications it is really going to be able to review. It has the resources to review far fewer applications than what it wants to receive.

As the agency thinks through these issues, I encourage it to think about exactly what it wants, describe in advance what it wants, why it wants it, what harms it is solving, how those harms will be solved, and also how many tests it expects to regulate and receive, and how it has the resources to do so. Thank you.

DR. GUTIERREZ: I want to thank all the speakers, and now we will break for lunch. We have an hour and a half. So we will be back here at one o'clock, at which point we will start with the second group of presentations.

I would like to say one thing before we go to lunch, and I would like to end with kind of the thought that began this first session. That is, really why we are here is to think about what is good for the patient and how do we do right by the patients. I will see you after lunch.

(Whereupon, the foregoing matter went off the record at 11:28 a.m.)

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AFTERNOON SESSION

Time: 1:01 p.m.

DR. GUTIERREZ: Good afternoon. Let's see if we can begin the afternoon session.

What we plan to do in the afternoon is continue with the public comments. We have, I believe, about eight before the panel meeting. Seeing that we only have eight comments, I think we probably can go ahead and do them, and begin the panel discussion, and we will play it be ear, and maybe if we need a break or interrupt in the middle of the panel discussion or right after the panel discussion. So why don't we go ahead and start with the afternoon.

MS. SERRANO: And our speaker this afternoon is Judith Wilber.

DR. WILBER: Good afternoon. I am Judy Wilber. I am an independent consultant working with Tethys Bioscience, XDx and many other companies with CLIA labs that offer innovative diagnostic tests as LDTs.

Many of these companies are members of the American Clinical Laboratory Association and the 21st Century Coalition for -- or Coalition for 21st Century Medicine.

I am also the CLIA lab director for XDx. XDx is

one of those few companies that has received FDA clearance for an IVDMIA. I have been working in all aspects of laboratory medicine for many years, starting at the San Francisco Department of Public Health, and then at Chiron and Bayer where we introduced new viral load tests through a CLIA laboratory as LDTs in order for the physicians to start being able to figure out how they could use an accurate measure of virus in plasma.

I would like to participate in the discussion of many aspects of LDTs in this session, but I am going to concentrate on clinical evidence requirements for moderate risk LDTs. Most of these comments will apply to traditional and de novo 510(k)s as well.

Clinical validity was defined in the recent draft AHRQ technology assessment report on laboratory developed molecular tests as the determination of test characteristics, clinical sensitivity, specificity, predictive values and likelihood ratios.

Clinical utility was defined as whether the results of the test can be used to pursue effective treatment or provide other concrete clinical benefit.

The objective of introducing new diagnostic tests is to offer better tools to clinicians and to improve the actual delivery of care. Innovation in laboratory medicine leads to

improvement in medicine as practiced, not necessarily improvements to the ideal practice of medicine.

While it is often pointed out that CLIA requires an analytical but not clinical validation of an LDT, every test must show accuracy.

So if the test system purports to diagnose a particular disease or predict a particular clinical outcome, a laboratory is going to have to demonstrate how it performs on samples from patients with that disease or with that clinical outcome. That must be done before the test is introduced.

Evidence criteria must also be realistic. Properly collected and stored, well characterized, retrospective samples can serve as prospective studies when the clinical outcome is known. Prospective outcome studies are not feasible when the outcomes may take many, many years.

Properly designed studies will define clinical test characteristics, but usefulness may be unproven when the test is introduced.

The objective in the 510(k) process is to evaluate analytical and clinical validity. Increasingly, there is a tendency in OIVD to require evidence not only of clinical validity, but also clinical utility or usefulness. This may also translate to LDT

oversight in the future.

The questions are: Is the test better than what is already on the market or what is currently available, or while the test may measure the level of particular analytes accurately and also predict outcome, will it change physician behavior and result in a measurable clinical benefit?

I suggest that these questions are best answered after the introduction of a test or postmarket. If a test is innovative, it might not fit immediately into standard patient care. Clinical utility and usefulness will be determined by medical practice, reimbursement, education, publications, engagement with experts in the particular medical field, acceptance, and ultimately practice guidelines.

Many of the most well accepted diagnostic parameters, such as what is the glucose level that should be used to diagnose diabetes, what is the hemoglobin A1c level that should be used to diagnose diabetes, cholesterol targets, and appropriate cardiovascular risk levels when using high sensitivity CRP? These were set by the field, not by the test manufacturers.

In summary, the clinical validity should be validity for 510(k)-cleared IVDs and moderate risk LDTs, and clinical utility will be established through postmarket use. Thank you.

MS. SERRANO: Our next speaker is Steve Williams.

DR. WILLIAMS: Thank you. Good afternoon, everybody, and thanks for the invitation to speak.

For those of you who don't know me, I have actually spent my entire career in discovering, validating, qualifying and defining best practices for biomarkers, surrogate endpoints, and diagnostic tests.

I have worked in big pharma, and I am working in a small diagnostics company today. I have collaborated with the FDA and with the NIH.

I have two concerns about the proposal to increase regulation. The first one is simple. If the increase in regulation leads to a delay in patient access to new tests, people will die. The second is that the language around risk and high risk is inconsistent and potentially flawed. I am going to explain what I mean.

The first one is through an example. If you take lung cancer, it kills over 150,000 people a year, but you can cure it if you find it early, but of course, you don't find it early in most people.

My company and a number of others are trying to

find blood tests that detect stage 1 disease when it is surgically curable. We have actually found what looks to be a promising set of proteins which will diagnose this disease early, and we think that the LDT containing this panel can be launched next year, and it will contain results from about 2,000 patients.

Currently, our FDA approval plans are about 18 months later than this. So if the LDT approach was to go away, this kind of delay would cost 590 lives a month or about 10,000 lives over the period of an approval, and you have to multiply that by the number of important tests that will be released over our lifetimes.

Now some of you are going to look at this and say he is just being over-dramatic. I am not being over-dramatic. This is a catastrophic and certain consequence of delaying the introduction of new tests.

Now the public who is still alive might say, we want more assurances; we want more quality; we want more data. But the people in this picture can't talk.

The second concern is about the targeted approach to high risk tests. What appears to be going on is that we have heard that maybe more regulation and higher evidentiary standards would be applied to important tests.

Now it pains me to say this, but this is entirely the incorrect approach. As I said, I have spent a lot of my time defining what good practice is, and good practice here is not to do best practice at all, but to do this.

If delay causes death, you cannot afford to maximize evidentiary standards. You have to satisfice. Satisficing is to seek a solution which is good enough, without seeking the best. I am going to show you how this might work in practice.

This is a world recognize tolerability of risk approach, and you can see this little chart. You look at the consequence of false results and the value of the true results of your diagnostic test.

Let's start with the false results. Here I think we are pretty aligned with what the FDA has been talking about. Results that have a high consequence -- where the error is of high consequence should have a high evidentiary standard. That is the righthand side of this box.

One major caveat, though. This is not absolute. It is a relative assessment. So this consequence is against the best available alternative, and we haven't heard that in the language so far. We have heard as if it was absolute.

For example, failing to diagnose cancer, a false negative error: One would think that that would always be high consequence, and it would be if there is an existing test that works quite well, and your new test is replacing that and making a new error. You are responsible for that new error. You killed somebody. But if there is no test available, the person would have died anyway. The consequence of a false negative error in that case is much less. In fact, it is nearly zero.

So these consequences are not absolute. They are relative.

Now let's look at the vertical axis, the value of the true result. We haven't heard anything about that in the background to this meeting. It is important.

If the value of a true result is high, the evidentiary standard should be low or lower. Why is that? Well, first of all, if something is very valuable, if the true result is valuable, you can tolerate more errors. The currency of public health, if you like: The more benefit you have, then the more errors you can tolerate.

The second reason is that, actually, if your benefits are much bigger than your errors, you need less precision. You don't need so much information and data to prove that your benefits are worth more than the errors.

Then the third thing is that, if you have an important test and you delay it, you may kill people. But so far we have heard from the FDA that the important tests are the ones where they are going to focus the attention. Importance seems to be synonymous often with the value of the true result, although as Dr. Mansfield pointed out this morning, the consequence of errors comes into play, but we have never seen this tolerability of risk approach to evidentiary standards.

So what we need to see here is: We have heard about the importance of a test and the indication like cancer. Neither of those is equivalent to risk. What we need to hear more about is the context of use and the fact that delay may have serious consequences.

I will finish up with an example. In the top lefthand corner, we have heard how cancer is going to be a high risk test. Well, cancer can be in the top lefthand corner.

If there is no alternative test to a new cancer diagnostic, the value of the test will be high, and the consequence of error will be low. So new cancer tests can live in the low evidentiary standard box, which maybe is the LDT route.

So in summary, I don't think the case has been made for increased LDT oversight. The harmful effects of

increased regulation are certain and catastrophic, whereas the benefits of regulation that we have seen so far are modest and hypothetical, and the risk based approach is inconsistent or flawed.

So recommendations: Please don't delay the introduction of important new tests to patients, and please get more consistent on the language and the principles behind defining high and low risk tests. Thank you.

MS. SERRANO: Our next speaker is Winton Gibbons.

MR. GIBBONS: Hi. We appreciate the opportunity to provide our perspective regarding oversight of laboratory developed tests. We believe this issue has significant implications for patient health, treatment, and safety.

I am Winton Gibbons, Senior Vice President of Business Development for Nanosphere, Incorporated, and today Nanosphere would like to address the need to apply a consistent process for deciding the clinical utility for the intended medical use of a diagnostic test, whether the test is a marketed laboratory developed test or a marketed manufacturing test.

The use of a common process for deciding clinical utility across both diagnostic tests and lab services will, first,

improve patient safety; second, reduce confusion among doctors, hospitals, and patients. This would increase the quality of health care while accelerating acceptance for medical proven diagnostic tests. Third, lower health care costs by making better, more consistent, and cost effective medical decisions.

Manufacturers will be able to develop and market tests with the same intended medical uses as those same tests developed by laboratories. Moreover, the laboratories will then have more options.

They can still develop the test themselves or buy the tests from a manufacturer. This flexibility will reduce medical costs and improve quality.

There are current examples of laboratory developed tests being offered for use in medical practice, while the FDA has stated that the clinical utility of those tests has not been proven.

Therefore, a diagnostic manufacturer would need to perform additional clinical work to show clinical utility for the intended medical use, the PMA that was cited earlier, and then submit for this premarketing approval, while lab developed tests do not have to do this.

The clinical utility and intended medical uses for

specific diagnostic tests are expanding more and more the unjust diagnosis, for example, to selecting specific drugs or procedures or assessing the safety of a given therapeutic or how a patient will respond.

There seems to be little scientific reason not to require practical approaches to confirming that specific test helped medically, as intended. Moreover, the same standard of medical proof should be applied to lab developed tests as those from IVD manufacturers.

This approach to proving clinical utility must be practical, as the diagnostic industry cannot afford clinical studies that are too costly and time consuming. But the clinical studies should be done, nonetheless.

Incentives must not be ignored for diagnostic manufacturers or laboratories to pursue new tests that may still need expensive clinical studies.

As a manufacturer of diagnostic tests, our business prospects are based on what we provide for our customers. We also know that most clinical labs have difficult budgets and don't have enough people, but it both of our jobs to make sure that we provide quality, clinical useful results, whether we sell diagnostic products or lab services.

Additionally, we understand that differences may exist in confirming the analytical performance for a laboratory developed test, if that test is used only in the lab that developed it; whereas, a manufacturer's test that is sold to many places could need to be validated more to ensure its analytical performance.

We also believe that there are still medical conditions that are too infrequent to bear the cost of more clinical studies, and can rely on clinical observations.

We do understand that developing LDT tests has likely both a time and cost advantage over following the manufacturer's FDA pathways. However, it cannot be assured that this speed and cost advantage translates into good medicine, if it lacks proof of clinical utility for its intended use by physicians.

What is needed is a regulatory process common to both FDA reviewed manufacturer tests and laboratory developed tests, proving the clinical utility of those tests. Currently, there is no single standard of regulations applicable to all.

Rather, laboratories are reasonably free to develop an apply new tests, including genetic tests, as they think appropriate, whether or not the FDA would accept that the medical data proves clinical utility.

As we see things evolving, new tests have arise through medical observation and put into LDTs on which physicians arrive, often without enough proof. This is particularly problematic when those tests are used to pick procedures or guide therapies.

Clinical risk and safety also plays a role in the type or thoroughness of proof that is required. These risks have to be taken seriously and addressed by clinical studies for each new use of an existing test and for each new test.

Our recommendation is that FDA policy should be scientifically based, dependable, and consistent for all providers of diagnostics. Well designed, clinical studies should be used to prove the clinical utility for intended medical uses for diagnostic tests.

These studies should be scientifically and statistically valid. We believe that it would be the FDA's role to create sufficiently detailed guidelines for these clinical studies or the determination of sufficiency of published clinical studies.

Moreover, we think that there needs to be objective third party expertise to make sure that the studies meet these guidelines and to review results, a role suited for the FDA. Thank you.

MS. SERRANO: We are going to just slightly rearrange the order of speakers. Dr. Bartlett is on his way. So the next speaker will actually be Mark Linder.

AUDIENCE MEMBER: Dr. Bartlett is here.

MS. SERRANO: Oh, okay. Well, even better.

DR. BARTLETT: Well, thank you very much for the opportunity to speak here. So I am John Bartlett. I represent the Infectious Disease Society of America, and this is a great opportunity for me to say a few things about something that has become very important to us in the field of infectious disease.

This is the convergence of two very real problems. One is the problem of the dearth of new antibiotics, and I don't think I have to tell this audience that problem, but I can tell you that last week I sent two men to hospice care. One was 37; one was 50 years old, otherwise in good health, but they had a refractory multi-resistant pseudomonas infection that we could not get rid of, and can't.

When we look at what is ahead, we don't see a light at the end of the tunnel. There hasn't been a new antibiotic, a new class of antibiotics for gram negative bacilli since the 1970s, and pharmaceutical companies just don't make them anymore, and don't intend to, as near as we can tell.

So that used to be our escape mechanism for the evolution of resistance, but now it has become really a daily encounter with what used to be easy to deal with.

The second is the example on the slide is where microbiology has gone. Microbiology has gotten farther and farther away from the bedside, so that now -- You know, back in the 1930s they made a diagnosis, an etiologic diagnosis of lobar pneumonia in 98 percent of patients.

So I asked Dale Bratzler this question: In your Medicare database, which represents the United States, how often do you identify the cause of pneumonia? And he said, on the basis of our experience with 17,3049 patients, we made an etiologic diagnosis that physicians reported in 7.5 percent.

We don't treat for pathogens. We treat for CAP or HAP or VAP, and part of the problem is that we cannot easily identify the pathogens.

So what we need are really two things. One is a way to get therapeutic trials so that we can identify the culprits of infection and enroll them in trials. The second is we need pathogen-specific therapy.

Part of the reason is that we need that in order to avoid unnecessary antibiotic abuse. But I can tell you, when you

are taking care of a bad patient they will show an increase in mortality rate for every hour that you delay the right drug.

So it is not all just antibiotics for colds and sore throats that represents an enormous part of the problem, which is antibiotic abuse, but a lot of it is just the necessity to cover everything that is there.

So my plea is to get the diagnostic tests out there. What is at the bottom of the slide is really some examples. I left off the most obvious one. What is the most obvious? It is probably HIV. One hundred million people on earth have HIV infection.

What is it, 99 percent of them were diagnosed by a point of care test that costs $20, and last year we can now say that the funding of the PEPFAR program saved one million lives, and this diagnostic test made that possible.

Does anybody think that more than three percent of the diagnoses in the rest of the world with HIV infection are made with anything other than a rapid diagnostic test?

So now we have got an almost perfect test for Clostridium difficile in terms of saying whether it is not there. The positive predictive value is probably about 100 percent, and we are using the MRSA test on hospital admissions, and influenza -- what a

godsend for public health, and the NAT test for GC and chlamydia.

There's plenty of precedents, but what we need are tests for the pathogens that we encounter every day and kill most of the patients that die of infectious disease in American hospitals.

So what do we want in these tests? Well, we want everything. We want them to be fast. We want them to be sensitive. We want them to be specific, and we want them to be cheap, and we have achieved that in some of them, and some of the examples I gave are examples where they are affordable. They don't require any machinery. They are instantaneously available. They are sensitive and specific.

So I think the examples are good in terms of being able to achieve these objectives. They should detect the pathogen, not the diagnosis. The diagnosis, clinical diagnosis -- that is what I spent six years of training trying to learn how to do the interpretation of the test.

Also, the specimen source needs to be defined, and there needs to be quantification for some pathogens, especially those that are associated with colonization by contaminants, and the test should be done in CLIA certified labs.

That completes my remarks. Thanks very much

for your attention.

MS. SERRANO: Our next speaker will be Mark Linder.

DR. LINDER: Thank you. I appreciate the opportunity to speak, and I can be brief as I have had a chance to comment earlier.

I am Dr. Mark Linder. I am with PGXL Laboratories. We are located in Louisville, Kentucky.

Obviously, this is a very complex issue that, arguably, there are gaps, I think, that exist in the structure. But ultimately, I think collectively in this room we all want to maintain the quality, integrity and availability of laboratory developed tests, and this has been echoed multiple times.

As I indicated earlier in my question to the panel, this seems to me to be focused and begins with the medical director's qualifications and training.

I would submit that there are mechanisms in place that can be leveraged to have maximal effect, and I would recommend that, as this process is evaluated, that one point of potentially focus would be to providing the regulatory infrastructure that would appropriately incentivize and guide the laboratory medical director, who is ultimately responsible for the

professional practice of their laboratory services.

So I list here some resources that I think could be applied to driving this, and again my point is to maximize the existing structure and focus this on giving the guidance to the medical director as needed.

I think that some considerations that need to be emphasized in this process is that, during the development of new statutes or regulations or structures, that the representation of laboratory medical directors is paramount to that. It is them who ultimately needs the guidance in making these choices and decisions.

I would think that our current structure, there should be good evidence to argue why they would need to exceed current best practices. I have indicated here norms on my slide, but I would like to reiterate that to say best practices.

Focus on protecting the interests of the patients to be sure that, if there are commercial incentives to development of new diagnostics, that those commercial incentives don't outweigh health care incentives to the patient. So we have to make sure we don't accidentally disincentivize the development of tests that will really be focused on the wellbeing of the patient.

Obviously, we need to reconcile, consolidate, and

clarify the regulatory authority, principally to give that medical director the appropriate resources and guidance they need to make the right decisions to treat their patients.

Again, I think many people have indicated that we would want to avoid disruption of current qualified activities, and recognition of current CLIA certified services. There should some accommodation for that.

Then another issue, I think, that has come up that I think will be paramount is there should be some allowance for postmarketing credentialing. I think that laboratories who are in good standing, that have a long history of appropriately putting laboratory developed tests into practice -- those labs should be able to continue to innovate and move forward, with there being some sort of a postmarket evaluation process being included.

So again, my major points are: I think that, if a structure was designed to enhance and to support the laboratory medical professional's responsibilities, it will actually create a lot of guidance. I think there's a lot of very good medical directors out there, and I think that many of the people have already reiterated some of the issues that I have brought up. So thank you.

MS. SERRANO: Our next speaker is Janet Trunzo.

MS. TRUNZO: Thank you. I am Janet Trunzo with the Advanced Medical Technology Association, also known as AdvaMed, and AdvaMed represents manufacturers of diagnostic products, medical devices, and medical information systems.

First, AdvaMed supports timely access to safe and effective diagnostics. We believe that regulatory oversight should be commensurate with the risk.

Further, AdvaMed wholeheartedly agrees that a risk-based approach to regulation should be applied to all diagnostic tests, whether developed by manufacturers or in clinical labs. Regulation should be based on the risk of the test, not on who happens to develop or make the test, and should be focused on the probability of harm associated with how the test is used in patient care.

A risk-based approach will concentrate scarce FDA resources where they are needed on tests that are unproven or that pose a high risk to patients, if results are incorrect.

A risk-based approach will also allow the focus of priorities and resources on important regulatory issues associated with personalized medicine and companion diagnostics.

AdvaMed has developed a risk-based proposal for an approach to regulating all diagnostic tests under risk-based tiers.

Fundamentally, the approach centers on the risks associated with a given test, as determined by several risk factors and any risk mitigations associated with each factor.

The first risk factor is how a test is used clinically. The key issue is the risk of illness or injury associated with misdiagnosis, false results, or no results.

The second factor is the degree of novelty of the analyte; third, the degree of novelty of the technology. Fourth is the level of training and experience of the operator.

Coupled with the risk factors are mitigation factors, and risk mitigation factors can include scientific evidence such as the availability of peer reviewed literature, general controls including quality systems and the inspections associated with them, special controls, consensus standards, FDA experience with similar devices, laboratory process controls, and user experience and training.

Using a decision model, risk tiers can be assigned by balancing mitigation factors with the risk factors. The decision model is patterned after FDA's Tier/Triage Guidance from 1996.

For example, by using this decision model, a new use of an established analyte or a new technology may not necessarily fall into a higher risk tier if appropriate risk mitigation

factors are available.

We also believe that well standardized, low risk tests should be exempt from premarket notification. The 2007 medical device user fee agreement included a commitment for both FDA and the industry regarding the exemption of low risk, Class I and Class II IVDs.

AdvaMed submitted a detailed rationale based on a scientific methodology for identifying these low risk tests eligible for the exemption. We believe that exempting low risk tests from premarket notification will free FDA resources to focus on submissions for higher risk tests.

For tests where premarket review is required, the risk of the test drives the data submission requirements. Application of this Tier/Triage decision model will help FDA, industry, and laboratories to identify these IVDs and the level of regulatory oversight that is needed.

Tests need not forever remain in the same tier under this approach. As the risk and benefit of a test becomes more well established, scientific literature may support a lower risk tier, a lower tier of regulation for subsequent premarket submissions. This flexibility frees up FDA resources for the more novel and riskier tests.

In summary, AdvaMed's risk-based approach recognizes FDA authority to regulate the safety and effectiveness of all diagnostic tests based on the benefit/risk profile, regardless of where the test is produced.

The approach adds objective, transparent, and standardized criteria for stratifying premarket regulatory data requirements, according to clinical risk and availability of mitigations, and it establishes a rational process for focusing review resources on products with highest or unknown risk.

Finally, our approach builds on the strengths of the current system and infrastructure to ensure the safe and effective use of all diagnostic tests. Thank you.

MS. SERRANO: Our next speaker is Sara Kenkare-Mitra.

DR. KENKARE-MITRA: I am Sara Kenkare-Mitra from Genentech, and on behalf of Genentech I would like to thank you for the opportunity to comment.

So I am going to go over four things, first talk a little bit about Genentech's position on personalized health care and patient health and safety. I would like to speak briefly about Genentech's Citizen's Petition around the regulation of in vitro diagnostic tests, and talk about the link between IVD tests and

patient safety.

At Genentech, personalized health care is at the core of our strategy to get the right drug to the right patient, and it is an integral part of our strategy to provide safe, effective and clinical differentiated medicines to patients.

In this context, IVD assays that provide information at a molecular level are key to the PHC strategy. In this context also, patient health and safety depend not only on the thorough evaluation of safety and efficacy of medicines used to treat patients, but it is also combined with an appropriate assessment of the accuracy and the clinical utility of IVD tests that significantly inform prescribing of drugs.

In December of 2008, Genentech submitted a Citizen Petition to the FDA which set forth patient focused reasons why the FDA should exercise its regulatory authority over IVD tests. Some lab developed tests are entering the market without review of evidence of claims made to support their use in patient care.

Additionally, we also presented a framework for using the FDA's current risk-based classification system for necessary and appropriate review of the LDTs. We believe that the LDTs should be calibrated to the risk posed by the test, so that it doesn't stifle innovation in personalized health care, but all

claims that are made should be scientifically validated and reviewed by the FDA to ensure that health care professionals and patients have access to validated diagnostics that can help guide their therapeutic decision making.

We believe that diagnostic tests are very linked to patient safety, and without appropriate regulation of all IVD tests, patients are at risk. Use of diagnostic tests that make unsubstantiated claims intended to guide specific therapeutic decision making do threaten patient health and safety.

We believe that the potential risks to patient health are not only that they don't receive the appropriate treatment, but also receiving inappropriate treatment, thus exposing them to unnecessary side effects or possible treatment failure.

We also believe that regulation of LDTs should be comprehensive, and it should include the analytical and clinical performance of the test, as well as monitoring of test performance postmarket in order to protect patients, so through postmarketing surveillance of adverse events and medical device reporting. And again I recall the example of the Vitamin D testing where patients were exposed -- There were inaccurate Vitamin D tests results that affected patients for over two years.

I would like to reiterate that our continued concern is patient health and safety. Today LDTs continue to enter the market without sufficient review of scientific or clinical evidence for claims made to support their use in patient care.

Manufacturers of LDTs promote their tests without FDA regulatory oversight, and also promote responsiveness to therapies without FDA review of data.

In contrast, as you know, Genentech identified biomarker which predicts responsiveness to therapy would require full regulatory review prior to approval of the test, inclusion in labeling, and any promotion or use.

Genentech is concerned that the current environment is unsafe for patients and possibly creates situations that could result in inappropriate treatment.

So in conclusion, with a focus on personalized health care, diagnostic tests have begun to play an increasingly important role in clinical decision making and disease management. Lab developed tests that have not been properly validated for their intended use put patients at risk.

Patient risk includes not only failure to receive the appropriate treatment, but receiving inappropriate treatment, and we believe that a risk-based application of FDA oversight to LDTs is

the appropriate approach to achieve the desired public health benefit. Thank you.

MS. SERRANO: Our last speaker for Session 1 is Saurabh Aggarwal.

MR. AGGARWAL: Good afternoon. First I want to thank FDA for giving this opportunity to come here and express my views on this important subject.

Second, I want to congratulate FDA and all the speakers for all the presentations, because I think that has really helped us understand this extremely critical technology which is, I think, moving quite rapidly.

Today I will be making a few comments as an observer who has worked in a lab, as a scientist who was developing technologies and, third, as an industry consultant.

I am Saurabh Aggarwal. I am a principal at Parexel Consulting. I help drug and device manufacturers with business strategy. I also write policy and strategy articles which I publish in two Nature magazines, Nature Biotech and Nature Reviews.

An important disclaimer: I am here by myself. I am not representing my company or any organization. These are totally my personal views.

So first of all, I want to voice my support to the previous speakers and presenters, that I totally agree, and I have a strong feeling that the medical science has made tremendous improvement in the past 10 years.

I think we have a number of new technologies which have helped and improved patients' lives quite dramatically. However, I think these technologies are very complex. I think there is some need of oversight and regulation, and I think the key question, which was mentioned earlier, is yes, there is a need for oversight, but how, how to do it so that we don't hamper innovation.

So in that context I want to mention first my observation as someone who worked in a lab and who has observed some medical oncologists ordering the commonly used tests, which is PSA test, and I was struck that something as simple as PSA test, which has been used for quite -- almost like several decades, that oncologists had to order it from two or three labs to confirm that the test is right.

I think that raises an important question. I am not saying that that is a trend or there is something wrong with PSA tests. I think it raises the question that what about, when we talk about complex tests, five, 10, 15, 20, 100 genes -- I would just

have asked -- There were presentations highlighting almost 400-500 genes.

So I think those are extremely complex tests. I think there we have to really understand how we can bring them in use in a confident way.

My second observation is as someone -- as a scientist who developed and used these technologies. I want to again reiterate that these are extremely powerful technologies, but they are very complex.

What I saw was even scientists who have been in the field for 10, 20, 30 years -- even they had challenge in understanding and interpreting the results of these tests. I think it is extremely challenging if we start communicating and presenting these genetic test results directly to the patients.

I will mention a key thing, which is: I strongly believe that, yes, 30, 40 years ago we had tests which were binary, zero and one, yes or no.

Genetic tests, or many of the new tests that are developing are not yes and no. I think there are many layers of analysis, there are many layers of interpretation which are there, which need to be understood and have to be very carefully communicated to the patients.

My third observation is as an industry consultant as working with R&D heads and several CEOs, and I want to just make -- express something which I didn't see for the last 10 years, and we are seeing for the first time, is a lot of confusion in the industry.

I want to just plainly convey that confusion, that R&D heads of several companies are confused about how they should pursue companion diagnostic or basically a biomarker strategy. I think it would be very helpful if FDA could either provide guidance or there could be some kind of advice to help them understand.

Lastly, I just want to make three recommendations, and these are very different recommendations, but I will still go ahead and, hopefully, they will add value to today's discussion.

Well, the first one is I would strongly recommend FDA to understand some of the best and the worst practices that evolved in the last 10 years. I think, in the absence of clear regulation, what happened was we saw this more than 20, 30, 40 or 100,000 technologies and tests which have come to the market.

There is a mix of best and worst practices. I would really advise FDA -- I'm sure you have done some kind of

focus groups or discussions, but it will be great to understand what is being done really well, what is being done really bad. I think that will provide us lessons of what we should do with these technologies in the future.

My second recommendation is -- I am actually local. I am a neighbor to both CMS and FDA. So I attend all the Advisory meetings, and in the past one year CMS organized three Federal Advisory meetings on genetic tests and on diagnostics, which were quite helpful, and they were really, I think, thought provoking.

I think there is a strong opportunity for FDA and CMS to work together on diagnostic tests.

A quick comment: I think just, if there is no formal regulation, I think the whole idea that CMS has to pay for these tests, the fact that there is a huge amount of paperwork which flows through CMS, could be an opportunity to collect data, analyze data, and have some kind of oversight.

The last quick comment -- this is more scientific comment -- is for the industry and maybe also for FDA, is something about controls. I felt as a scientist that controls play a big role in fine tuning both the efficacy and the safety of these tests.

I think that we might need to think how we can have smarter controls, positive and negative controls, so that these tests, not just for their approval but for continuous monitoring and testing, so that doctors and patients have full confidence in what they are using. Thank you very much.

DR. GUTIERREZ: Okay. We are going to move then into the first panel. So I am going to ask that the panelists please come up, and I am going to ask the moderator, Brenda Evelyn from the FDA who is going to be moderating the panel, to come up and to introduce the panel members, and begin the panel discussion.

MS. EVELYN: Thank you, Dr. Gutierrez. Good afternoon, everybody. Welcome to our panel discussion on patient and clinical considerations of FDA oversight of laboratory developed tests.

Again, my name is Brenda Evelyn. I will be moderating. I am from the Office of Special Health Issues at the Food and Drug Administration.

Our panelists this afternoon are, to my left, Colonel Alan Magill, Director of the Division of Experimental Therapeutics at the Walter Reed Army Institute of Research. Then we have Dr. Steven Gutman, who is an Associate Director of

the Technology Evaluation Center of Blue Cross and Blue Shield.

Next we have Dr. Paul Radensky, an internist and partner in the law firm of McDermott Will & Emery, and our final panelist is Cara Tenenbaum. She is Vice President of Policy and External Affairs at the Ovarian Cancer National Alliance, and we heard from her earlier today.

What I would like to do is to start our discussion by focusing on some of the questions that the agency raised for this particular panel, so that you can hear perspectives from these panelists on those issues, and we will also try to explore some of the points that were raised earlier today. Then we will open it for discussion for the rest of you who have questions as well.

I just want to mention that we won't be discussing any product-specific issues or laboratory or manufacturer issues, and that the questions that will be best addressed tomorrow in tomorrow's sessions with regard to clinical laboratory challenges or direct-to-consumer testing or education and outreach -- we won't go down those paths at this particular panel. We will save them for tomorrow.

So our focus, again, will be the patient and clinical considerations. So with that, I will pose the first question to the panelists, to each of them.

So I would like to know what might increase FDA oversight of laboratory developed tests? How might those affect patients and clinicians? What benefits might thee be to patients and clinicians for the products to be regulated?

So maybe -- Dr. Gutman, maybe you might want to start?

DR. GUTMAN: Yes. Well, in the days I used to hang out in FDA, and certainly in the places I hang out now, people are interested in the same core value, which is good science. Good science should be ubiquitous. It should -- Maybe the regulatory threshold should be different, depending on the rarity of the disease or on the risks of the disease, but good science and transparency of that science is really critical in my mind.

I think that is what FDA has to offer, that it has to offer -- I am beguiled, and I thought FDA was very generous in suggesting many things on the market are not really very enthusiastic about self-regulation. I don't know how well that worked on either Wall Street or in the Gulf.

So I would be a proponent of suggesting that the core should be good science. It, obviously, should be risk based. There, obviously, should be concerns for protecting important technology, protecting rare diseases.

I would actually argue that the HDE is an underutilized resource. It doesn't get any easier than that. So for rare diseases, I hope no one is worried, and that it just is common sense. It just is common sense that an intelligent regulatory approach is based on risk, however you may argue about risk, rather than on business model.

It seems to me the argument forward should be focused on what products are riskier enough that FDA should be paying attention to them.

MS. EVELYN: Thank you. Would any of the other panelists like to comment on that? How might increased FDA oversight of laboratory developed tests affect patients and clinicians? Cara?

MS. TENENBAUM: Hi. I addressed this a little bit earlier this morning, but I think that, certainly for my organization, we use the FDA approval as kind of a Good Housekeeping stamp of approval. Things are approved by the FDA, and my organization -- we don't endorse any tests or product or drug.

So to say that something is FDA approved means a lot. I think that there is also some regulation in terms of interpretation, what things mean, all the labeling guidance and all

of those, so that patients understand what the test means, what the results mean.

I think, from my perspective, that can be confusing, and as I said this morning, I am not sure what it would mean for clinicians, for a doctor to face a patient and have to kind of try to put the toothpaste back in the tube or convince a patient that maybe that is not the right test.

I know they have a lot of that to do, but I think along with FDA approval comes a fair amount of educational materials that are very important for patients to help understand what their test means.

MS. EVELYN: Thank you. Dr. Magill?

COL. MAGILL: So a first point is I just should have a disclaimer. Obviously, I am in uniform as an Active Duty Officer, but these are personal views and not any views of the Army or the Department of Defense.

I think I would take a little bit follow-on from the previous speaker. There is a certain qualification of these assays that one assumes with an FDA either clearance or approval process.

I think that fact alone is very poorly understood across the clinical and patient community, the difference between

clearance and approval and what that might mean in terms of prospective clinical trials or clinical utility. That is just, I think, an issue with diagnostics in general, but I think, if there is a benefit to increased FDA regulation of at least certain in vitro diagnostics, it would be in that sense of a better qualified test, so that clinicians who, by and large, may be very busy and not have access to all of the information to assess an individual diagnostic, would have that third party review, which I think, certainly, could be very useful in many settings.

MS. EVELYN: Thank you. While you have the microphone, Colonel Magill, I would like to ask you: In general, are physicians aware that a given diagnostic test might not have been cleared or approved by FDA, and how that might knowledge affect their clinical practice?

COL. MAGILL: Well, and I hesitate to speak too broadly for such a wide community, but I think, in general, from what I have seen -- and this is certainly across the board in any health care system, both domestic and international -- I think there is not a very good understanding of what it means to, quote, "have a well characterized diagnostic," have an assured manufacturing and quality control systems, and then how to interpret the result.

I went to medical school, shall we say, a few years ago, and I certainly got no training whatsoever at that point in time. I don't think things have changed dramatically since that time, and one acquires this information in a variety of settings, and this probably is very discipline and educational setting specific. But in general and in practice, often a diagnostic test result is either a yes/no or a quantitative number, and the real understanding of performance characteristics, false positives, false negatives and such, is variably understood.

MS. EVELYN: Thank you. Dr. Radensky, I am interested in your perspective on that question.

DR. RADENSKY: Sure. I think, also being thirty-plus years out of medical school as well, I am afraid I also come from a time period where there wasn't a lot of training or discussion about the regulatory underpinnings of any laboratory tests.

What I would say, though, was important, at least in our training and how I functioned as a clinician, although I haven't been practicing for a number of years, is that you are looking at what type of information you need. What is the clinical question you have, and you are relying on the laboratory and whatever regulatory framework that the laboratory has to get

the answer right.

I think often, in terms of, at least historically, in terms of being able to interpret what the test meant, we often relied on what we knew or what was in the literature about translating the analytical validity into the clinical validity.

I would say that, looking 20-30 years ago when we had HIV and there were a lot of issues that we had and questions we had about immune markers, I recall quite clearly that we would send specimens out to a laboratory in California. We had no expectation that those tests were cleared or approved by the FDA. We were really looking at what was the information that we wanted to get, what was the best information to make decisions.

MS. EVELYN: Thank you. Does anyone else want to weigh in on that question? If not, I will move to the next question, which perhaps Ms. Tenenbaum or Colonel Magill or even any of the panelists might want to respond to.

What would be some of the reasons? You sort of hinted on it just now, Dr. Radensky, but can you give us a little more information about what some of the reasons are that a patient or a physician might choose a lab developed test over a cleared or an approved FDA -- FDA approved, I'm sorry, cleared or

approved in vitro diagnostic?

MS. TENENBAUM: So I am not sure that patients would know or care. I don't care what my tests are. My doctor orders them, and they are the ones I get that he or she says I need. So whatever the approval process is, I think that is a little bit behind the curtain for the average patient.

I also don't know that a patient generally is the one choosing these tests. They may advocate to go into the doctor and say, you know, I need this test or that test, I saw it on TV, or what have you. But unless we are talking about the direct-to-consumer tests that they can get in the drugstore, I am not sure that the patients have that much of a say in them.

So whether they are approved or cleared or laboratory developed, I think patients want the best tests, and I think that, when their doctor recommends that they get a certain test or requires them to get a certain test for their treatment or for their disease, I think we assume that it is right. I just don't think that we assume that much of a margin of error. So I am sorry to give a really simple answer.

MS. EVELYN: Thank you. Dr. Radensky and then Dr. Magill.

DR. RADENSKY: I think again, coming from an

internal medicine perspective where, really, what our training was, was to go out and get the best information to be able to make a management decision for the patient, we were also taught that it was our responsibility to figure out the best source of that information or the best surgeon to do a procedure, the best device to use as a heart valve. Our training was that that was our responsibility in internal medicine to make those decisions.

So the way I would look at it is that, if you had a test where the analyte and its clinical meaning were well known to you and that that was something where it was well established, then what you are looking at is what are the available laboratories and where could you get a test that will produce that result reliably and accurately.

I think the question that comes up, and often in the context here, is where you have a new analyte that perhaps physicians aren't familiar with.

I think the same framework pertains, whether it is FDA clearance and what would be there on an FDA clearance information or a summary of safety and effectiveness for something that would go through a PMA or something that is an LDT is what is the evidence behind it, and how can we be confident both in knowing both the benefits and the limitations of the test so

that we would know how to use it in clinical practice.

I don't know that per se that it is any particular regulatory threshold as much as it is the evidence that is behind it that is really critical.

MS. EVELYN: Colonel Magill?

COL. MAGILL: I think that first question of reasons why one would choose to use a laboratory developed test is simply availability of a test, of any kind of test.

I have been an infectious disease trained physician and do most of my practice now in the area of tropical infectious diseases. So almost by definition, all of those would be -- in this country, would be rare, and we have very few sort of FDA commercial approved tests. So it is simple availability.

In that setting, it is frequently looking at confirming an etiologic diagnosis, either a pathogen -- and these are almost always through send-out molecular tests. If there is a culture available, you will either do it in your own laboratory or it won't be done, or some sort of serological assay.

I think many clinicians who think about this would like to have some sort of third party validation, if you will, a peer review. You know, why would you read or believe a journal article in a medical journal that had not gone through rigorous

peer review? So you would say an FDA qualification process or some other qualification process that would give you that peer review would be highly desirable.

MS. EVELYN: Okay, thank you. I want to follow up on something that came up earlier in the presentations today, and I think Dr. Radensky talked about it is the information behind the test that people are seeking, and Colonel Magill, you talked about availability of the test. But what we heard this morning was that underutilization rather than overutilization of laboratory developed tests is the norm until the tests are accepted by the medical community.

So I am interested in what spurs the physician, the community, the medical community, to accept a laboratory developed test? Is it the claim that the test purports or is it some type of peer review process? Is it that it eventually will get a clearance or an approval from FDA? What is it that physicians are looking for in terms of when they will accept a lab developed test?

DR. RADENSKY: I think it will vary widely, depending upon the practice environment and where a particular physician is located. Certainly, in academic centers you learn about the availability of new tests on rounds or by learning from

grand rounds or journal clubs, and going through what is the evidence for some new test. You learn by talking with your peers about who has used it and what has happened with it.

Out in the community, it can be the same, although my guess is that it is somewhat different if you are not in the same environment on a daily basis with folks going through the literature. But at least historically, it really was you learn about a new test, and you want to find the evidence.

When I was in training to diagnose a heart attack around 1979, we used LDH and CK. In the early 1980s, we switched to CKMB. By 1990 we switched to troponin. In each case, we learned because of what was in the literature, like the GUSTO study came out and really showed how troponin could be used in diagnosis and management of heart attack, and you pick up from the literature, from experience and talking to your colleagues.

MS. EVELYN: Thank you. Colonel Magill?

COL. MAGILL: I think that is actually a pretty interesting question. That really trends into medical practice and how do you actually do what you do in a setting of patient care.

I think you ought to learn about some of these new tests and what they potentially could do from claims of

manufacturers and such. I think there is -- Initially, it is sort of a reluctance necessarily to believe that up front, and you really want to, I think, looking at peer review, colleagues, journal articles, and patients. In this day and era, patients often are the ones -- first ones bringing to your attention certain new testing procedures and availability.

Then I think from a clinical perspective, it is what can this do for me? You know, what kind of actionable information? Is this going to allow me to treat or not treat or curtail duration of therapy or choose different therapies? If you can directly relate back to something of good patient outcomes, then I think it is much more likely to be incorporated into practice.

Then I think, certainly, of course, availability. If you are working someplace and your laboratory won't offer it, doesn't offer it and won't pay for it, then, of course, that is obviously not something that is going to be introduced or used.

MS. EVELYN: Thank you. When you mentioned what can you do with a test, it brings up the utility aspect. We heard a lot today about analytical validity, clinical validity, and clinical utility.

So I would just like to ask the question: What are patients' and clinicians' expectations with regard to clinical

validation?

Then a follow-on question would be, and perhaps, Cara, you might want to address this: What do you think the impact would be on patients' understanding and acceptance of a test for which true clinical utility has not quite been demonstrated?

MS. TENENBAUM: So I think that we should actually start with utility, and then work backwards from there. I think that, if there isn't anything to do with the results of a test, it is not nearly as useful, even if it was 100 percent accurate. So just in the interest of limited resources, that is where I would focus.

I think -- I was talking to the genetic counseling folks who are here today, and I think that we have that issue with, for example, BRCA1/2 mutations, for which women with a family history of breast and ovarian cancer are tested, and it tells you your likelihood of developing breast and ovarian cancer, and for a number of these women they might change a monitoring or screening strategy with their doctor or they might choose to have prophylactic surgery. But even if you are positive for the mutation, it is not 100 percent.

So there are a couple of genetic mutations that

are 100 percent, and you will get the disease, but likely it is some sort of propensity.

So I think that we deal with these fuzzy areas, and I think that, for my organization, certainly, we recommend that people see a genetic counselor, because those people are specially trained to interpret these results and help you figure out what the utility is: Why are you asking this? What will you do with the information? What will you do now that you have the information?

So again, what it means to patients is the important thing.

MS. EVELYN: Does anybody else want to give a perspective on that? Dr. Gutman?

DR. GUTMAN: Yes. I think clinical utility is a little like beauty. It is in the eye of the beholder, and that you can have two sets of people look at the same data and come to somewhat different conclusions.

So the deal here is that it ain't easy, and I don't mean to disparage my colleagues in medicine, but I think the average physician is poorly trained to actually use old lab tests, much less cutting edge new lab tests, and that that actually speaks to whether you leave the existing system, you modify it a little or

you modify it a lot toward the need for transparency.

I personally think the IVD web page and for all of the Office of Device Evaluation summaries of safety and effectiveness, having access to the actual data -- Maybe there are people who actually do read that data and use that data in decision making. That data doesn't exist in a laboratory developed test. Maybe it should. I don't know. Maybe the registry at NIH will take care of that.

MS. EVELYN: Colonel Magill?

COL. MAGILL: I think that issue of clinical utility, which I often just translate into that initial statement of intended use, is really very important. I tend to focus on the unmet medical need, being in the public sector, but if you are in the private sector, it certainly is an unmet medical need, but it is also, I think, the commercial potential.

You know, most folks aren't in business to make something that will never sell anything. So I think marrying up those two from the private sector is very key. You can have great commercial potential, and if at the end it really doesn't address an unmet medical need, it probably isn't going to have a great future.

So in some ways, that is an initial decision before you start developing or going down the pathway to develop a new

laboratory test.

MS. EVELYN: Thank you. I want to follow up on something that Dr. Gutman just raised about physician training, about what some of these tests might mean.

So the question is: How might increased FDA regulation of laboratory developed tests affect physician training, such that they are able to understand what the results mean and explain it to their patients? Anyone?

DR. RADENSKY: I definitely concur with Steve, that our training was fairly limited in terms of understanding diagnostics generally. There was some effort to understand biomedical statistics, and included within that were how to look at diagnostic tests, but I think many physicians -- Steve is quite right -- would be confused between sensitivity, specificity, and positive and negative predictive values.

I do think that there are two key pieces of information that would be helpful, regardless who the regulator is and how the information comes out to physicians. I think one is understanding what does the test show, and how does it translate to clinical endpoints.

From a clinical perspective, it really is positive and negative predictive value, because you have a result, and you want

to know what that means. Sensitivity and specificity are very useful, but you don't know in the population you are dealing with whether or not they do or don't have it. So you really are looking at the predictive values.

There was some early understanding of Bayes' Theorem, but I think that is much more in medical training today than it was back 30 years ago. So that the first is really having better information out there for the docs, not just a, yes, it is cleared or, no, it is not cleared, and this is just what the indication for use is, but more information more directly out there to the physicians about the underlying data supporting the clinical information.

Then second is how to use it. I myself don't like terms like clinical utility and clinical validity, because I think they end up getting a lot of political overtones to them that hamper the discussion. But I think it really is a question of what are you going to do with the information?

Are you going to take the information? Is it going to change something that you are going to do in terms of diagnosis? Is it going to change something you are going to do in terms of management?

I think, if anything has driven physicians there, it

has been the reimbursement profile, because I can tell you, I trained prior to the DRGs. DRGs came in at the end of my training, and our training was do everything that would have some marginal benefit, because it gave more information.

A dramatic switch with the change in the reimbursement system that then said, really be able to show what the incremental benefit is. Again, I think providing that information on the incremental benefit of one test over other information that physicians would have would be critical.

Again, regardless of the regulatory framework, I think those are the critical pieces of information that are necessary.

MS. EVELYN: Thank you. We heard from Ms. Tenenbaum earlier that in her experience many of the patients don't really know or understand the difference between those tests that are regulated and those that are not. But I would like to pose this to the physicians that we have on the panel.

What has been your experience with regard to what the patients think about the tests, whether they are regulated or non-regulated? Do they know? Do they care? Have they expressed opinions, in your experience? We might start with Colonel Magill.

COL. MAGILL: I think the simplest way to respond to that would be that the kinds of responses are as diverse as the patients you see. There just clearly are people who can walk in the door. They know far more about this than you do, because they have spent the last two months of their life reading about it, and they are very familiar with these issues.

Then there are other folks at the other end of the spectrum that are not as familiar, and are really looking to you as a physician or a group of health care providers to provide guidance, and that they really are very trusting in the sense that they say, well, what would be best for me? What is your recommendation?

So I think that, at least in this -- Maybe that is a reflection of the metro area around here where you have a very diverse and well educated and well versed patient population. So, yes, I think there are certain groups out there that are very familiar with this, and then I think it goes back to this qualification piece. How well qualified are these assays for the intended use, and there is a wide diversity.

MS. EVELYN: Thank you. Dr. Gutman?

DR. GUTMAN: No, I think that is it.

MS. EVELYN: Okay. Nothing to add to that?

Dr. Radensky, nothing to add? Okay. Thank you.

We heard earlier today, too, that laboratory developed tests were actually different from in vitro diagnostics and should be regulated differently. Others say that maybe they should be regulated the same way.

So in your opinion, what makes a laboratory developed test different, and why should it be regulated differently or the same? Dr. Radensky?

DR. RADENSKY: I think you have to break apart the components. If you are looking at the question of what is the clinical meaning of the analytical result -- so what does glucose mean? -- then I think there should be no difference between a laboratory developed test and an in vitro diagnostic test kit.

It is taking that information, and what can I do with it, and the evidence base that can support whether it is a new test, whether it is an IVD or an LDT, I think, would be the same in that regard.

The underlying getting to analytical validity and the some of the quality systems, I think, would be different, because there are differences between something that would inherent in one lab and produced in one lab versus something that would be a kit and distributed out. But I think what often, at

least, is my understanding, a lot of the concern that has been raised has really been about the level playing field with respect to the need for clinical data to translate the analytical results or the clinical result, and that, I would think, would be the same for both types of tests.

MS. EVELYN: Dr. Gutman?

DR. GUTMAN: Yes. I can only echo that, not only as a regulator and someone who now does assessments for third party payer, but as a patient advocate, as a person who, unfortunately, knows what it is like to be a health care consumer.

I think, form the patient's standpoint, what they want is a test that works. Doesn't matter to them whether it is home brew or -- excuse me -- a lab developed test or whether it is commercially distributed. It is does the damn thing work? That is really what counts.

I actually think that, if consumers actually understood what was going on, at least some of them would be horrified.

MS. EVELYN: All right. Colonel Magill?

COL. MAGILL: I have to say that thinking on this and sort of modulating it a little bit by the comments I have heard this morning, you know, I think there is a wide variety of practices

out there, and I think one of the previous public commenters made a very good point about trying to capture best and worst practices, so to speak, to get some sort of idea of what really is the problem and then what is being done well in that setting.

It sounds as though we have an environment in which actually capturing that information is not as straightforward as one might think. So getting an assessment of what maybe is -- what are the real problems that need to be corrected is one good step forward.

Then I think the real question is: It seems like there is broad general consensus that everybody would like access to an accurate diagnostic test that is ready tomorrow when you need it, and it is successful and relatively -- and it is at least affordable in some setting, and that certainly, the innovation and the driver in a less regulated market is tremendous.

So we are trying to balance those needs and retain that, and yet still get a quality diagnostic. I think, from a physician's perspective, most of the time, you know, you do send off a request to the laboratory.

The patient goes to the laboratory, and blood is drawn or something is done. The specimen is either worked on in-house or sent out to a big commercial laboratory, which is then

often sent to a smaller specialty laboratory, and a result comes back.

All of that, from both the patient and the clinician's perspective, is somewhat of a black box. The assumption is everything is going well, and I think that is the question here. Maybe the assumption -- maybe it isn't always going well.

Then what level of regulation is needed or desirable to improve that status quo, I guess, would be the question.

MS. EVELYN: Dr. Gutman?

DR. GUTMAN: Yes. Again taking it from the patient's standpoint, you tend to lose perspective when a loved one becomes ill. I actually don't object to half-baked tests. In fact, there might be circumstances where I would want a half-baked test on myself or a loved one.

I do object to calling it a real test when it is an investigational test, and I think that there should be an effort at more transparency in labeling or honest marketing, so that if a test is really being offered in a place where it might have some incremental value to people, I say give it to them, but give it to them honestly. Make sure it is labeled as an investigational

product and, even better, make it an IDE so there is some responsibility for at least a modicum of data gathering.

MS. EVELYN: Thank you. Ms. Tenenbaum?

MS. TENENBAUM: I think we are getting back to the issue of reliability and decision making. I think that that is really important. But one thing we haven't touched on yet is: We talked about the value of FDA regulation, but we haven't talked at all about the issues that it could pose to access, and we have all talked about that.

We all -- you know, free, cheap, easy, reliable. But you know, adding another layer of regulation could impede that, whether that is price or time to market. So I think those are also things that we need to consider.

MS. EVELYN: Dr. Radensky?

DR. RADENSKY: I would follow up on both Steve and Cara's comments. I think that, from a treating physician perspective, another key feature is having information that is timely.

If you know that there is something that is out there that might be helpful, recognizing that there are limitations in the data but that you could have access to it today and that it might be helpful in decision making, but the best scientific study

would take another 10 years to get the results, which is realistic if you are talking about prospective controlled trials in some early stage cancers, then as a clinician I think you make the decision, and patients as well, that you are willing to use imperfect information in making a management decision today; because you may not have the 10 years in order to make that decision.

Again echoing Steve's point, I think, really, what is critical is having labeling and information that goes to the treating physician and the patients that is more than a yes/no. It is more than a limiting statement that says we don't know how this works in treatment selection but, really, what do we know, and what do we not know.

That is what, I think, really would be very helpful for treating physicians and patients.

MS. EVELYN: Dr. Gutman?

DR. GUTMAN: And I hope you would do that with informed consent.

MS. EVELYN: Okay. I want to move on to the next question, and shortly we will open it up to the audience for some questions as well. As the audience is thinking about their next question, Ms. Tenenbaum, I wanted to explore a little bit more about the issue that you raised.

You must have been reading my notes, actually. But the question that I had was: We have heard a lot today about use of laboratory developed tests that might give us a wrong diagnosis or having the wrong treatment or no treatment. But I wonder about, is there an economic impact that we need to think about for patients and physicians?

I know this will probably come up in tomorrow's session about the economic impact maybe on clinical laboratories. But do any of you want to comment on what might be some economic consequences to patients or physicians as a result of either physicians ordering or using a cleared, approved test or a laboratory developed test? Dr. Gutman?

DR. GUTMAN: Well, right now it is my impression that the connection isn't particularly strong. So FDA can clear or approve tests which third parties may decide are not ready for reimbursement and, certainly, the reverse is true. There are laboratory developed tests that FDA hasn't cleared or approved that are being reimbursed.

So I think, at least at this point in time, the correlation probably wouldn't make it through an FDA 510(k). But whether there should or shouldn't be more correlation, I will leave to the other members of the panel.

DR. EVELYN: Would anybody else like to respond? Are there economic consequences for patients and physicians that we need to consider?

COL. MAGILL: I think with any -- you know, the decision to order a diagnostic test, somebody pays. The question is -- rarely, the physician. I have never seen that. So the physician is not going to pay for the diagnostic.

So sometimes indeed the patient does, and we know that there are a variety of settings in which patients can either pay directly by the Internet or a variety of factions. So they pay out of pocket with no hope of being reimbursed by anyone.

Then there is a variety of third party payers, insurance companies and a variety that would pay. So I think there is an impact, and I would assume that most third party payers would prefer to reimburse for high quality tests that are going to improve medical care, and would be much less willing to pay for tests that have an uncertain pedigree, if you will.

MS. EVELYN: Thank you. Ms. Tenenbaum?

MS. TENENBAUM: One thing that I think we are hoping will come out of some of these tests is targeted therapies, and we heard about that a little bit today, and there are some on

the market right now. But as we move forward with these co-developed tests and treatments, the hope is that they actually save time and patient -- I don't know what the word is, but improve quality of life. Don't give patients treatments that wouldn't work for them or that aren't useful for their specific disease.

So, hopefully, there are some positive economic impacts for some of these tests. I think that -- I think Dr. Gutman touched on people with insurance, but let's not forget, there are some people without insurance, and there may be until about 2014 -- keeping my fingers crossed. But there are also people -- For example, I had a woman who called me.

She wanted to get just her CA-125, which is a blood marker, to monitor her recurrence, and her doctor made her come in, and she couldn't afford another doctor's visit. So it is not just the test. It is the doctor's visit. It is getting to the hospital, paying for parking. I mean, there are a lot of patient costs associated with these.

So I don't want to ignore the toll that it takes on the full patient and their family.

MS. EVELYN; Thank you. Thank you for that. Okay, I would like to open it up to the audience. So if you have

questions, would you go to the microphone and give us your name and your affiliation, and present your question. Yes?

AUDIENCE MEMBER: I would actually like to make a comment with respect to cost, because -- So one of the reasons that clinical laboratories do set up their own tests, even when commercial tests are available, is because it is less expensive, and the imposition of FDA regulation isn't going to increase the reimbursement for laboratory tests.

So laboratories would have two choices, either potentially lose money, or more money on a test, or discontinue offering that test.

I think we really need to be careful here in suggesting that somehow imposing, for example, on academic medical centers what would be an enormous regulatory burden is cost free.

MS. EVELYN: Thank you for your comment. Yes?

MS. EPSTEIN: Question for the panel: Do any of you believe --

MS. EVELYN: I'm sorry. Could you give us your name and your affiliation, please?

MS. EPSTEIN: I'm sorry. Alice Epstein, CAN

HealthPro.

MS. EVELYN: Thank you.

MS. EPSTEIN: Do any of the panel members believe that a physician, an ordering physician, prescribing physician, should be held to a different standard when ordering a laboratory developed test versus a commercially available test? Thank you.

MS. EVELYN: Anyone? Dr. Radensky?

DR. RADENSKY: Well, I think the standard that you would have with performance of any procedure is the standard of what is acceptable in the community as a medical malpractice standard, the standard of care.

You have also associated with that the standard of care with respect to what you inform patients, what Steve was talking about before. That standard actually varies across the states.

A little more than half the states, it is very similar to the professional malpractice standard, that what you tell patients is what is the standard of care in the community for physicians telling patients. In about 20 of the states, it is really what would patients find material, and that, I think, might be a question. But I think it really would be, again, a question about

not just the issue of a regulatory yes/no, but what is known about the test and how is the test used, and what are physicians doing? But there are different standards currently that we have between what patients would want to know versus what the physicians typically tell patients.

MS. EVELYN: Thank you. Colonel Magill?

COL. MAGILL: That was actually a very interesting question. The same thing came across my mind this morning as I was listening to comments.

I would say there is a perspective here. One would be if you are prescribing a therapeutic or a drug. And of course, that is a fairly black/white: Approved or it is not. We really have three settings. You could choose to use a non-approved drug, if you thought that was the best option.

Then there are varieties of treatment INDs, investigational INDs, single patient use. There are pathways to obtain that, if you thought that was the best drug for your patient.

Then, of course, there is FDA approved on-label use, which is the typical standard, and you would just proceed. Then there is the off-label use of an FDA approved drug, which I think, increasingly, many people are now, if not going to informed consent or at least informing the patient that this is an off-label

use and here is why you think it is the right thing to do.

So to carry that paradigm, which I think is a little more accepted, into the diagnostics role, I think, would be quite new, and it is not quite so simple. But it is a provocative thought.

MS. EVELYN: Thank you. Yes?

MR. BIGGERS: good afternoon. My name is Greg Biggers. I am a citizen of these United States, and as such, one of the employers of the FDA. I am an individual engaged in my own health, and I am occasionally a patient of clinical providers.

My question is this: We have heard a lot today about concepts of intended use, of accuracy, and of utility. I wonder what our opinion is about the concept of adaptability of assays, such as a genome sequence which may be valuable for some decisions that we know today, and will probably be valuable for many, many more decisions coming in the future. How does that concept of adaptability play into the decisions we need to make in this context?

MS. EVELYN: Does anybody want to tackle that one?

DR. GUTMAN: Yeah. Well, that is a particularly tough one, because the science is what it is, and you can't make --

You sometimes can't make gold out of hay.

So there was an interesting piece in the New England Journal of Medicine in the last couple of weeks about the challenge of that.

I think it really is important that whatever FDA does -- and FDA has a long history of trying to be flexible and trying to be malleable, certainly, in the 510(k) program. I can't imagine a more malleable program than that, because you can make changes and make decisions on your own that, again, if the consumer understood, some might not be entirely pleased.

I do think the issue of adaptability is important, and I think that, if FDA moves in some direction, whatever that creative direction might be, whether it is collaborative with CLIA or outside parties, whether it is on its own, that it does build in the ability to move rapidly when circumstances call for it.

FDA is struggling -- Unless it has changed since I have left, it is struggling against a formidable workload, but when the chips are down and a really important decision has to be made, and collaboration with a company has to be made, I think the track record is impressive and that it will do what is right for the public health.

MS. EVELYN: Thank you. Yes, sir?

DR. EMANCIPATOR: My name is Ken Emancipator. I am a pathologist, and let me emphasize it right now. I am speaking as an individual and not on behalf of any organization.

I want to say that this morning I was actually delighted when I was listening to Courtney Harper's presentation where she acknowledged the clinician/pathologist/patient relationship, and that was back in the good old days when, you know, regulation of laboratory developed tests was not an issue.

I have been listening very closely to this panel discussion in the past few minutes, and I haven't heard the word pathologist mentioned once.

I think traditionally, the traditional role of the pathologist has been to help the clinician understand the nuances of diagnostic testing that, I think, Andre Astin from New York State was talking about, that clinicians do not understand.

So if I get to the point here, the issue: I am actually very concerned that, if FDA gets into the business of regulating laboratory tests, that traditional role of the pathologist would be gone forever, and I would really like to see the Public Health Service take actions that would encourage to restore that traditional role of the pathologist, rather than to have government

regulation replace it.

MS. EVELYN: Thank you. I would like to ask one of the panelists to respond to that, because I think that also ties into the question we had earlier about the level of education that might be required for physicians to be able to interpret these tests, and the relationship.

Would that really be gone if FDA regulated the tests? Would those relationships between pathologist and physician disappear? Thank you, Dr. Radensky.

DR. RADENSKY: One of the areas that I know has been of concern to me is that insofar as FDA would take oversight of laboratory developed tests, and recognizing Liz's point this morning that FDA would regulate tests and not labs, it would cause the laboratories to be medical device manufacturers, and that is a key point that would be different from the IVD model currently with a distributed IVD where it is sold to a laboratory, and you have a laboratory. You have a medical director. You have a pathologist there to speak to.

One of the things, I think, that would be critically important is that that relationship that one can have with a medical director in a laboratory or talking to the pathologist at a hospital, if it is sent out to another laboratory, that that be able to

be maintained, and in particular, as the laboratory would assume a role of a medical device manufacturer, that that flow of communications, which under CLIA is substantially more proactive than it is as a medical device manufacturer responding to a request for information -- that that be something that be very carefully looked into and very carefully addressed so that that flow of information is not shut down.

MS. EVELYN: Thank you. Colonel Magill.

COL. MAGILL: I would like to -- That was a great comment, and I certainly would like to endorse that. That is really just a key example, whether it is anatomic pathology and you are going to see the pathologist or radiology and you are going to see the radiologist, or clin micro, this concept of the clinician can talk to a specialist in that area is really just a key event.

Actually, not so much FDA regulation of outsourced tests, but I think one of the biggest threats to that is the continued sort of loss of capabilities outside of the major university medical centers. It is very expensive to maintain, for example, a clinical microbiology laboratory with well trained professional clinical microbiologists.

What I have seen is that that asset is shrinking by the month, and that those tests are simply sent out to the big

feeder laboratories, if you will. So I think there is a threat to that relationship, and I am not so much sure that it is due to -- that it will be changed that much by FDA regulation of tests.

MS. EVELYN: Thank you very much. Yes, sir?

DR. MIDDLEBERG: Hi. My name is Rob Middleberg. I am the lab director at NMS Labs, a lab known nationally for esoteric toxicology testing.

I know you didn't want to bring up any specifics but I have to, to get to the patient part. It is not really a specific.

Toxicology testing, by its own nature, is episodic and situational. Things happen. The World Trade Center collapses. maybe there is a hypothetical leak of oil in some large body of water.

A lab like ours gets a call that says can you develop a battery of tests for people, workers who are being exposed to oil or 11,000 World Trade Center rescue workers. Can you do something for them?

We say, yes, we can. We can do the tests. We have some of them. Some of them, we will develop. It will take us three months to develop and validate. Now we will send them through the FDA, and probably in about a year and a half, we will be able to offer the test to you.

Well, by that time, specimens are no longer valid. Analyte stability is poor, and I am not sure how you address this to the patient. It is the patient who wants the test, and as Dr. Gutman said, I will take a half-baked test as long as all the caveats are known and recorded.

That is often what we will do, as you are the limitations of the test. I think the patients need to understand or be explained how this is going to happen, or told, yeah, there is a test, but you can't have it.

I think, if nothing else, it will make a good 60 Minutes story, but I think we all want to try to avoid that. So the question is, how do you explain this to patients ultimately?

DR. EVELYN: Okay. Dr. Gutman?

DR. GUTMAN: Yes, I think you underestimate the fortitude and resolve of not just our office, but of the people working at FDA. If they hit with the circumstance and you are forthcoming, and you interact with them, they will get the damn thing out yesterday, if that is what it takes to protect public health. At least, that is what they used to do. I can't imagine they have changed.

If it, in fact, helps but you are not quite there, then the deal is that you do negotiate some kind of investigational

labeling or you can do an EUA. You can ask Dr. Hojvat. She can do things in six days instead of six months. She can do things in 24 hours. She has staff who will stop sleeping and work all weekend.

DR. HOJVAT: Absolutely true.

MS. EVELYN: Thank you. Yes, sir?

MR. SNELGROVE: Hi. Ted Snelgrove from Crescendo, but representing myself today.

This is about patients and doctors and understanding of these tests this session, and one of the things, I think, FDA should consider -- I would love the panel to respond -- is how language is used.

So FDA has fastened on this language of device regulation for what are clearly outside observers services. By continuing to focus on these as devices, everybody outside the Beltway who doesn't have a JD gets confused, because they are clearly not devices even by the definition put up this morning by Dr. Harper, which identifies tangible products that you can hold in your hand or ship or something.

So these products are information based. They ought to be regulated in the context that recognizes that they are information, not tangible things that go back and forth to these

doctors form these labs, in the cases where that is, in fact, the case.

If in fact, you were to create a new regulatory regime, maybe develop a new center like CBER was developed in the Eighties focused on information based products that actually creates a regime that is focused on how to regulate information, that might be a much better solution and actually more understandable to people outside the Beltway than trying to shove information products into a hole designed for tangible products, which is creating all kinds of problems, and I guaranty you, we haven't even seen 10 percent of those problems yet if this is the path that FDA decides to continue to pursue.

So I know it is what the lawyers at FDA wanted to say, and I know it is because that is where they statutory authority, but they can get other statutory authority, and I would support them in doing so in order to regulate appropriate information based products in a way that is appropriate for information. We could get into more detail of that, but I think that is the key thing.

I think it would go along way toward breaking down the lack of communication between the agency and the public because of these legalistic terms that defy logic outside the Beltway, and I will leave it at that.

MS. EVELYN: Thank you. Ms. Tenenbaum. Yes, go ahead.

MS. TENENBAUM: Thank you for that. I think that what I said before, and I didn't intend to be flip about patients not caring whether it is an IVD or a lab developed test, it was the same kind of thing. I mean, what is the difference? At the end of the day, we want to know the information that we need to make good medical decisions.

So whatever we call these tests, however we regulate them, whether they are different or the same, you know, at the end of the day we need reliable tests that give us the information we need to make good medical decisions.

MS. EVELYN: Thank you. Yes, sir?

MR. BONELLO: Hi. My name is Bill Bonello. I am an industry analyst that follows the IVD industry.

I guess a question that I have for the panel: It is pretty clear form the discussion that we are about to embark on a major increase of regulation from the FDA.

I am just wondering, as we think about the big picture, are any of you aware of any evidence beyond simply what is anecdotal that there is a significant problem of physicians and patients being provided with diagnostic information that isn't

clinically reliable or rigorous as a result of lab developed tests?

MS. EVELYN: Good question. Someone want to try that one?

MS. TENENBAUM: Sure, I will take that one. There have been a couple of tests where results have not -- the right results haven't come out, and there have been a couple of tests, I think, that have come to market without valid data to back up the tests, and I think that the FDA has acted quickly to address those issues.

I think that the industry in some of these cases has also acted quickly to get patients the right -- if they mixed up test results, to get those. But, certainly, we have seen that tests do come to market without Phase 3 data, without good data, without knowing that there is utility.

We have certainly had patients with ovarian cancer who have been told that they do or don't have ovarian cancer, and that has been wrong. So they have had surgery or decided not to have treatment based on the results of a faulty test.

MS. EVELYN: Dr. Gutman?

DR. GUTMAN: The other source of data -- I don't know if New York State plans to publish it, but they certainly mentioned it this morning -- is the fact -- and I suspect the FDA

experience would reflect that as well -- is that often in the regulatory process things that aren't kept off the market are actually improved, the claims made more honest, the performance made more clear as a result of the interaction with the regulatory body.

That may not be as sexy as heading an overt problem, but without doubt in my mind, that contributes to the quality of health care.

MS. EVELYN: Colonel Magill.

COL. MAGILL: Yes, I think people's experiences are going to probably be fairly narrow and siloed based on what they actually do. So I could comment on malaria microscopy that is done in hospitals around the country, which generally is quite variable quality, a series of point of care anthrax tests that were pushed into a commercial space several years ago that proved to be essentially useless. But again, I think these are fairly narrow.

I think one of the concepts I got today was that that is really sort of an unknowable at this point, and it may be because of the lack of a registry or some other venue by which to get that quality information.

So I would agree. Getting a sense of the scope of the problem would be quite useful.

MS. EVELYN: Dr. Radensky.

DR. RADENSKY: I think one of other piece that this points to, again from a treating physician perspective, you need the information that is going to be actionable. So when you are looking at a labeling claim, if the labeling claim is something that really is not on point with how you are going to use the test, whether it is FDA cleared or not, that is not all that helpful for the treating physician.

One of the areas that, I think, is very important for FDA and the stakeholders to explore is how we can make sure, especially in the context of a laboratory developed test where, again, the laboratory would be the manufacturer, that the claim is, in fact, what will be useful to the physicians; because turfing most of the use to be an off-label use is not going to, from the treating physician's perspective, be anymore helpful than not having any cleared claim.

MS. EVELYN: Okay. Thank you. Yes?

MR. HARDING: My name is Gary Harding, 30 years of experience in performing applied research evaluations in medical products and as a consultant.

My question relates specifically to the underutilization and the overutilization, things that we talked

about this morning, as well as the presentation by one of the FDA folks about what data is provided in the databases that are available in the FDA system.

It specifically related to the summary information that results for the studies that are performed in order to approve or clear these devices.

For the treating physicians on the panel, is you are given the opportunity to access just summary information and that summary information is only what the FDA chooses to synopsize of what actually occurred in evaluating those products, if you cannot get that information, the full information, any other way other than to request it from the manufacturer and wait for them to respond or choose not to respond, or to get them by filing a Freedom of Information Act request and having all of the information take quite sometime to reach you, as well as being blacked out in some cases, is that information actually useful to you like peer review, clinical data in the Journal of American Medical Association in making some decision on whether you should utilize that test or not?

MS. EVELYN: Thank you. Someone want to respond? Dr. Radensky?

DR. RADENSKY: I think that the current

summaries certainly have some information that is quite useful, and it varies, for sure, when you are looking at a Vodkin case summary versus a summary of safety and effectiveness for a PMA.

But I think that is why many of us are very encouraged by the prospect of having the NIH Gene Test Registry, and looking forward to collaboration between NIH and FDA so that more useful information can get out to treating physicians and to patients to understand the science that are behind the tests, to understand in what populations the test work, where evaluated, more information about the laboratories.

I think it will be very, very helpful, and I know that groups like -- I work together with a coalition, and we submitted some comments in about the scope of what we think would be very relevant fields, and I think that they are fields that would be relevant for treating physicians and patients, and expand substantially from what we currently have in some of the summaries.

MS. EVELYN: Colonel Magill?

COL. MAGILL: Again, I think that was a very useful comment, and I think it gets to the heart of what is the actual data and the quality of that data that people would use to assess a diagnostic, and then also who would actually do the

assessing, if you will.

I think the vast majority of clinicians are spread too thin across too many areas to dive into that data at any great depth. I think even, say, a typical, very well meaning investigator or clinician is not even going to look at the summaries published by the FDA, and instead will be looking at practice guidelines, for example, from their own professional societies and potentially from peer reviewed journals.

Having been on all ends of that spectrum, both sort of as a clinician seeing patients, as an investigator conducting trials, filing data to the FDA, and writing articles and reviewing articles, I can tell you, there are huge weaknesses at all points of that compass.

At a clinician's level, most of the time you are just saying, well, what is the best test for hepatitis C antibodies. Just tell me which one to use, and you are looking for a third party -- could be the FDA or another party -- to help you make that assessment, sort of like a Consumer Reports, if you will. I think that is really what most clinicians would be looking for.

MS. EVELYN: Thank you. Yes?

MR. VORHAUS: Hi. Dan Vorhaus, Robinson, Bradshaw and Hinson, and editor of the Genomics Law Report.

I would like to ask the panel to look a little bit into the future as we move into a era of increasingly multiplex testing and whole genome sequencing, and you have patients and physicians being asked to deal with increasingly broad sets of data and data that is maybe already in possession of a patient or in a patient's medical record or the consumer comes in with it.

What do you think the regulation will or should look like of interpretations of that data where you are not dealing with a single test, a single diagnostic test, but you are dealing with a much, much broader set of information and a number of, quote/unquote, "off-label uses" or interpretations that you could make of that?

Will those still look like traditional diagnostics to you as clinicians or as thinking about what the regulations should look like or are we going to need a different model for that?

MS. EVELYN: Who would like to try? Okay, Colonel Magill.

COL. MAGILL: Yeah, I will give a start. I think -- Yeah, I kind of sort of see a transition to a little bit of a new model. I am not sure the quote of a diagnostic, which in mind just brings up the single analyte, single solution, if you will.

Getting into this broader area of multiplexing,

which is really multiple pieces of information being generated that all may have to be interpreted together, I think that is an area where everybody is struggling a bit, both manufacturers, consumers, clinicians, health care systems in general.

So I don't have a particular answer for that, although I don't think it is going to look like what it does now.

MS. EVELYN: Anyone else?

DR. GUTMAN: Yes. I think the best you can do is try and address that in adjusting your regulatory threshold and having good labeling, but the problem is that, until you have the science to support a claim, you are just playing in a sandbox with no sand.

MS. EVELYN: Anyone else?

MS. TENENBAUM: Thank you for your question. I think the previous question also touched on this, which is the fact that I hope that this guidance or this new regulatory scheme will be forward looking.

I think that we are seeing that we may be getting data that we are not really sure what it means, and maybe we will know what it means in the future. I think that what we want are some regulation and a regulatory scheme that allows both industry and patients to react in the future, and that it is flexible

enough that, as our science does develop, because we know it will, that our regulations can keep up with that.

M.S EVELYN: Okay, thank you. Yes, sir?

DR. WRIGHT: Hi. Alan Wright, Caris Life Sciences.

I think my question builds on the last question. Personalized medicine has started a community trend where the subpopulations to be treated and analyzed continue to decrease in size. So that a clinical scenario where 10 or 20 years ago would encompass tens of thousands of individuals, now encompasses a few thousand individuals.

We talked a lot about ovarian cancer earlier in the day and targeting therapies for ovarian cancer. When you actually break that down and look at the clinical scenarios that those women face, there may only be a few thousand patients in that cohort.

The question is: What would be the utility of orphan diagnostic status, similar to orphan drug status, for the FDA review for these particularly rare conditions?

MS. EVELYN: Dr. Radensky.

DR. RADENSKY: Well, Dr. Gutman mentioned before that there is, in fact, on the device side a regulatory

framework for rare disorders. It is very different from the orphan drug, the humanitarian device exemption process for humanitarian use devices, but that is one mechanism that is out there.

Now that is limited to 4,000 per year incidents, different from the orphan drug 200,000 prevalence, but it is a mechanism that is out there.

I think that you raised, though, an excellent point. Is there something in between what we have on the HDE side and something like what we have on the orphan drug side that might be appropriate to consider as a regulatory model?

One thing there I know that has been a struggle on the drug side is exactly the point you raise. If you have something that is a fairly common disorder, lung cancer, but as you get to various molecular markers you get very small subsets, what does that mean from a regulatory perspective? Is the orphan drug approach appropriate for each of those subsets?

I don't have an answer to that question, but it is something that, I think, is important to be dealt with. But I think what it raises, again -- and I am coming at this thinking through it from the treating physician perspective -- is needing information in a timely fashion that is flexible enough to recognize the patient

population for whom you are going to be using the data.

When that is a very small population, you need to be more flexible in terms of the types of study data that might be available. I think that that is something that inherently FDA is familiar with and has grappled with, but I think thinking through those tools and being able to apply examples and seeing if we need new approaches on the diagnostic side are quite appropriate questions to struggle with.

DR. WRIGHT: Yes. This would be a rare situation in a common condition rather than a rare disease.

MS. EVELYN: Thank you. Yes, ma'am?

DR. REVELL: Hi. I am Paula Revell. I am from Texas Children's Hospital and Baylor College of Medicine.

I just wanted to go back to the concern about the timeliness of this proposed review process. I do clinical diagnostics for microbiology and infectious diseases. Recent memory with H1N1, we lost our first patient in April, and the availability, even with the emergency authorization, was months later.

So I am trying to get at the timing for some of these things can be critical, and I think if we take away the option to have -- Our test was appropriately verified and validated, but it

was still considered LDT or home-brew.

So had I had to go through the same process that Roche did or whoever did, you know, would I have been able to give anybody a diagnosis until September? I mean, these are the concerns that we have.

MS. EVELYN: Thank you. Does anybody want to respond to that comment?

DR. GUTMAN: Yes. I don't know the actual times. I think they were damn good, and I think that you can only do what you can do with the data that you have.

I think, if you had had -- and if it came with a credible dataset, that the FDA would stand on its head and have it out in the case of a critical situation like this within days, if not within hours.

I personally had at least one product while I was at the FDA that went out in six hours. So I just can't believe that, if the circumstances dictated, that our work group can't be responsive.

You do need to have credible data, but again I would argue that, if you don't have credible data, even that should go out. It should just go out honestly as an investigational device rather than as a full fledged "I am a real IVD."

MS. EVELYN: Colonel Magill?

COL. MAGILL: I think there were maybe two points there. One would be specific maybe on H1N1, and I don't think that there was a huge delay in the regulatory release of products, but there was certainly a delay in getting the appropriate reagents and qualifications, just getting the test ready, and that doesn't happen overnight.

I think your bigger issue is one we didn't really talk about today, was in response to novel or emerging threats, which are mostly infectious, but then I am biased in infectious disease.

I think this is a difficult area, because if it is a new and emerging threat, obviously, there is no predicate. There is nothing, and it all is going to be being developed and implemented in real time.

Again, I think currently the best strategy is to have Sally or somebody's phone number on speed-dial and start working with them very early, because I think in general, that has been our experience. They have been very willing to help in getting that going.

MS. EVELYN: Thank you. Yes?

DR. KAYYEM: Hi. I am Faiz Kayyem from

GenMark Diagnostics.

This conversation about leveling the playing field between LDTs and IVDs is already complicated enough. So I shudder to add another dimension, but in the arena of companion diagnostics I have gotten myself quite perplexed, and perhaps you can help me to understand how this level playing field might relate to another set of standards.

If we say we want to raise -- to level the playing field, we want to raise the level of standards for what clinical utility is and what the quality of data is, that is great. But the standards on the drug labels are really a completely different standard, safety and efficacy and outcomes, very high standards for drug approval. But other information that can go on the drug label, I think, has quite a low -- I don't even know what the bar for approval there is.

You are encouraged, I think, as a drug manufacturer to recommend certain diagnostic tests: Look at the HER pathway; look at the EGFR pathway; look at the drug metabolism genes; and this information might be useful.

So in a world where we have a level playing field in LDTs and IVDs and they all have demonstrated high clinical utility before something is approved, how will the future physician

deal with the fact that he is also being told that this other information is important, information that might not have risen to the level of clinical utility necessary to get an IVD or future LDT cleared?

MS. EVELYN: Okay. How will the physician interpret that? Dr. Gutman?

DR. GUTMAN: Yes. Well, I think there are two separate problems, and that to mix them together, it is a red herring. So I think the FDA needs to get right what is appropriate in terms of regulating an IVD, regardless of the business model.

So it has got to get that threshold right, and whether it should go up or whether it should go down, whether it should be resource driven. That is what this meeting is about, is to get input from stakeholders on how to titrate that.

I think that the co-development, the companion diagnostics piece, is -- It is irrelevant to me as a patient whether it is lab developed test or whether it is a commercially developed test.

What is relevant to me as a patient, is there the right amount of information to use the drug, and I would confess that it is from both inside and outside FDA. FDA needs -- can do, and needs to do a better job. I think they are struggling with that

and working on that. And although that is not the point of this particular meeting, if you have great ideas on how FDA can do a better job in that, I would write them in anyway.

MS. EVELYN: Dr. Radensky, I do want to emphasize that we want to hold this discussion to the impact on the patients and physicians. So when we are talking about level playing field, if we are getting more into the clinical laboratory and what that means for them versus industry, that will be discussed tomorrow. But go ahead.

DR. RADENSKY: I think that the point that was being raised with respect to what is on the drug labeling and also some of the discussion this morning in some of the presentations -- I don't think that most treating physicians would understand what goes behind the decisions as to whether or not mention of a test is in different parts of the labeling and what that means on the drug label.

I think that that is an area where greater education and outreach -- I think a couple of things. One, perhaps more clearer articulation of the standards and the criteria is one that would be helpful, but also greater education and outreach to the physicians on those points, because I don't think physicians do fully appreciate when they see something on the

drug label where it is and what the meaning is intended to be behind that.

MS. EVELYN: Okay, thank you. Yes, ma'am?

MS. STRATTON: Good morning. My name is Elise Stratton. I am representing myself. I just had a follow-up question for Dr. Gutman, who was referring earlier to the HDE pathway being underutilized and just wanted to understand -- I am not currently aware if the laboratory developed test has undergone the HDE review process, and what patient populations do you feel could benefit most?

Is there a candidate in mind that you have for what would be an ideal HDE pathway?

DR. GUTMAN: Yeah, I am actually not sure I can recall whether there has been an HDE that was based on a lab developed test or whether they are all commercially distributed.

I was using HDE as an example of a package, and again FDA is thinking out its future process. So it is looking at its past processes. It is looking at great ideas from people sitting in this audience.

One of the things it has done is it has made a deliberate accommodation for rare diseases, as Paul suggested. The numbers are quite different than in orphan drugs. There are

4,000. It is actually 4,000 tests per year, not 4,000 disease cases per year, but it allows for one of the most remarkable regulatory passages you can imagine.

It allows a product to go out essentially based on analytical performance and some presumption of a clinical validity, but no evidence of clinical validity. So it doesn't get much easier than that.

It does require a cautionary labeling. It requires some monitoring of volume of sales. It requires, I think, some cost constraints. You can't make a fortune off of this. I think you can recover costs. So there accoutrements that may or may not make it more or less attractive, but it is something FDA could look at it as it is trying to address the very real issue of how to deal with rare diseases.

I don't think the agency wants to stop testing of rare diseases. They essentially said that this morning. They have said that on other occasions, and I don't think that the agency can necessarily solve the science.

If there is only a handful of poorly documented cases, they can't -- again, they can't make gold out of wheat. So they can only do what they can do, but it is an idea that is appropriate for only a subset of products, but for those products,

at least my experience has been that it works okay.

MS. EVELYN: Thank you. Yes, sir?

DR. DAVIS: Bruce Davis, Trillium Diagnostics. Earlier today I was reminded by a Canadian colleague that we have, the most expensive health care in the globe, and certainly, when you look at quality indicators or outcomes, most of which this country doesn't make the top 10.

My laboratory colleagues, particularly in Europe, are very quick to remind me they do quite well without CLIA, without FDA. So I am just wondering, with this additional oversight, is this going to bring us closer to those quality systems or what are we missing here?

DR. GUTMAN: You are missing the fact that in Europe they won't pay for anything. So they essentially -- You know, they have the CE mark. They have -- At least for IVDs, they have administratively beautifully written requirements for their products, which is that all their products be traceable to standards, and they don't enforce them administratively well at all.

So on paper it actually makes more sense than what we do. It is as rigorous in some ways, perhaps less rigorous in others than what we do. But the bottom line is they ration.

DR. DAVIS: So are you saying the

commoditization as we have here is the difference?

DR. GUTMAN: Well, I am not sure I understand. Commoditization -- I think -- I do have an opinion about commoditization, but I am not sure it is healthy for me to express it. But, no.

You know, in Europe the countries that aren't routinely doing mammography or doing it with less frequency, they are countries that aren't PSA screening. I think that they are being much stingier in what they are willing to pay for and much -- I actually think that there is regulation. It is just not called regulation. It is called very tight reimbursement.

MS. EVELYN: And I think that is a question that perhaps we might explore a little bit deeper tomorrow. Thank you for your question. Yes?

MR. EITNER: Yes. My name is Casey Eitner. I am with Expression Pathology.

Earlier this morning, I believe immunohistochemistry was characterized as simple and well defined, and I think that laugh probably sums up the fact that it is far from simple and well defined.

As a matter of fact, some of the most public reports of failures in laboratory tests have related to

immunohistochemistry tests for estrogen receptor and HER2, and they were done with FDA approved kits.

By contrast, we are still waiting for the first approvals for kits for k-ras mutation and EGFR mutation, and yet in the last three or so years thousands of patients have benefitted from the availability of those tests as laboratory developed tests in treatment decisions relating to anti-EGFR drugs, and the FDA itself thought so much of the value of those tests that it actually had the labeling changed, as did European authorities, for the drugs to take into account the availability of the tests.

So I think that is a pretty good lesson to learn. I mean, it is easy for us to look at the bad apples and at the problems, but we have to look at the plus side to lab developed tests.

For me, one of the things that that underscores is that lab developed tests -- Frequently, technologies are not ready to be promulgated to large market in the form of products, but in selected laboratories that know what they are doing, have developed the test and can offer the test well, they can provide significant value.

One of the problems that I see is not providing for that intermediate risk, that intermediate category of tests

between a full blown commercial product that can be regulated and a test that could be done well, not half-baked -- well by a specific laboratory is it will stymie innovation. It will stymie the availability of these tests to patients well before they are ready to be commercialized and regulated on a large scale.

So I urge that consideration be given in the formulation of these regulations to that intermediate category that has been essentially the source of a lot of these very useful tests. Thank you.

MS. EVELYN: Thank you, sir.

MS. SNELGROVE: Hi. Ted Snelgrove from Crescendo. As you think about this from the patient and doctor perspective and you think about how they perceive results they get from either an LDT or an FDA approved kit, they may want to think about the information in the same way.

The assumption has been going on today that it is always better or preferred that this be done locally, that there is an advantage to having this done locally.

While that may be true in some cases, it is not universally true, and I think doctors and patients would agree that there are many cases where companies that are providing LDTs actually interact directly with doctors, directly with patients, talk

to them. They often have assignment of benefits and have to walk through the whole claims process.

They are there to answer questions about the test and test interpretation in a protected doctor to doctor scenario that allows a great deal of detailed discussion in a consultative way that is helpful.

That is very different than the kind of thing that happens when a kit test shows up in a lab that does hundreds or thousands of tests. Somebody does that and then explains what that simply means to a doctor.

That isn't necessarily superior. In many cases, simple tests can be more convenient and definitely more appropriate, but it isn't always more superior for a highly complex test or things that require a lot of preparation or work.

I think it goes back to how -- The same thing happened in the drug world in the last century when compounding went away and the drug industry started consolidating to do test development -- I'm sorry, drug development around simple products, and that allowed a lot of critical mass to come together to fund research.

The same thing is happening in this field, and it would be important to think about how it will play out over time,

and not make assumptions like it is always best if it is done locally, or else we would still have compounding happening in pharmacies for all these compounds, and drug companies would just sell supplies.

MS. EVELYN: Thank you for your comment. We are going to move along a little bit here. I am going to take one final question from the audience, and then I have one last question. At that point, I will turn it back over to Dr. Gutierrez. Sir?

MR. BIGGERS: Hi. Greg Biggers, still a citizen and employer of the Federal Drug Administration. I would like to apologize to the panel and the audience for not asking a concrete enough question my first time at the microphone, and I would like to get a little bit closer to the crux, if I may.

Sometime in the next six months, I expect to have in my possession a whole genome sequence for myself, six billion of these As, Cs, Ts and Gs and their order and location and which ones have been repeated and deleted and all these kinds of things.

In the near term, I expect that to be useful for answering some health questions now. I also expect those As, Ts, Cs and Gs -- and I will make a mention about them -- to be useful to me for questions we don't yet know the answer to, but will over

the next 20 years.

So what I am seeking this afternoon is just a few more nuggets of sense about how you might effectively regulate and why you might regulate my access to that data, those As, Cs, Ts and Gs that describe a portion of myself, not knowing what they might be useful for in the future.

MS. EVELYN: Thank you. Someone want to respond? Yes?

MS. TENENBAUM: I think it is really important to recognize that you and every person owns their own genome, and that is your own information, and I think it is great. I think that the complicated part of it gets to -- and I hate to, you know, be a broken record, but what do you do with that?

So you are saying that there is some information now that will be useful and some information that will be useful later. So we are talking again about, you know, medical decision making. I assume that is what you are talking about, not what shoe size you are going to wear when you are 15. So --

MR. BIGGERS: That time has passed.

MS. TENENBAUM: Right. So you know, when you talk about medical decision making, I think that it is important that you do that with a trained professional who can help you, and

I don't know what the regulations are going to look like in terms of that, if they are going to speak to that at all. But there are a lot of questions, and just because you have some mutation and you have a likelihood or a propensity doesn't mean that you definitely will develop a disease or that you need to intervene in any way.

So again, I think that it is really important that patients -- and again, I do think this is their information -- are able to interpret that in a meaningful way and make good decisions for themselves.

MR. BIGGERS: So my plea to you all then as you go and deliberate about this is very simple. If you do choose to regulate access to that type of an assay, please make it clear why it is in my best interest for you to place that barrier in front of me seeing that data. Thank you.

MS. EVELYN: Thank you. Okay. I am going to just pose one last question to the panel, and then we are going to wrap up, and I thank you all for being willing to participate, and I thank the audience for such an engaging question and answer session this afternoon.

So my final question to the panel is: From your perspective, what is the ideal? What would patients and clinicians like to see FDA do in this regard? Do you have a sense

of that?

We have heard a lot of different models. We talked about risk-based regulation. We talked about registries. We saw some different models presented in the public session today. So do you have a sense of what is it that you would like to see FDA do eventually? Anyone. Dr. Radensky.

DR. RADENSKY: Well, I think coming up with a regulatory framework that will provide, as we said before, timely information to treating physicians and to their patients so that they understand what and how are the guts of the test, and what and how it should be used, that whatever the regulatory framework is that is set up recognizes the difference in the nature of a diagnostic test from other medical devices, that recognizes and can adapt to the changing and exploding science that we have, and that also, like in meetings today and through other appropriate regulatory venues, allows for important stakeholder input so that the regulated community and those that rely on the products from the regulated community know what the rules are, and then know what to expect.

MS. EVELYN: Thank you. Anyone else? Dr. Gutman?

DR. GUTMAN: Well, I think that the biggest

challenge that FDA will face in however it progresses will actually be in the risk assessment, because the risk assessment is difficult. When SACGT was making its recommendations, it went through a number of iterations trying to get risk assessment right, and it had some of the best and brightest minds at the table, and they had great difficulty.

So I would like to see FDA, certainly, make decisions based on risk rather than on business models, but I would like them to make those carefully so that it uses its race horses wisely.

MS. EVELYN: Thank you. Colonel Magill?

COL. MAGILL: Yes. That is a little bit of a loaded question, but also the -- Interestingly, you know, most of the specialty diagnostics that I access in tropical infectious diseases are not FDA cleared or approved, and never will be.

I mean, there is an extremely small volume market there. If there was any regulatory burden, even the smallest speed bump, if you will, the test would disappear overnight, because no one is going to apply resources to a test that generally can hardly pay their return.

So I think that is a real risk moving forward, and I think Steve's comment was right on, and that there's limited

resources. Getting a well qualified diagnostic with the sufficient data that one needs for a de novo 510(k) or a PMA is not a trivial task.

It is a significant investment, and that if there is going to be a regulatory barrier put in place or regulatory move to make products better, that that is factored into some sort of a volume and impact. You know, we are going to get the most bang for our buck, if you will, in terms of a regulatory.

I also think -- and this may be true across the board with everything FDA does -- that this simple concept that it is either cleared or not cleared or approved or not approved -- Maybe we are -- and I am speaking completely on my own here. Maybe we are beyond that, and that this really is a question of an entry level "approval" which may be nothing more than a notification of intent to market with subsequent evaluation and subsequent additional approvals or reviews based on intended use.

So that you can have an idea of what is out there, and then on the left end of the spectrum, these really are literally just marketed as LDTs with very little information to go with it, all the way to full blown PMAs in which we have a great deal of confidence in the performance parameters.

MS. EVELYN: Thank you. Let us thank our panelists very much for participating today.

Dr. Gutierrez, I will give it back to you. Thank you.

DR. GUTIERREZ: So I do want to thank our panelists for a really very lively discussion.

I think what we would like to do now is actually just end here today. We will begin tomorrow, and what we will do tomorrow -- we are going to try to move things a little bit faster. So we are going to start at eight. I will not take the full 15 minutes to have an introduction, and we will probably shave a half-hour from lunch.

So we are shooting to try to end tomorrow around five, so people can make flights and stuff. So I guess that is all for today, and see you tomorrow morning.

(Whereupon, the foregoing matter went off the record at 3:26 p.m.)